Chapter 31
What are the current approaches to non-hormonal male contraception?

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Experimental non-hormonal male contraceptive approaches do not rely on the administration of hormones or compounds that block hormone secretion. Non-hormonal male contraceptives may have some advantages compared to hormonal male contraceptives as they avoid any impact on testosterone concentrations and therefore would be less likely to alter sexual function, sex drive or body composition and would not prevent participation in high-level sporting events that exclude the use of exogenous androgens. In addition, oral delivery may be more feasible with non-hormonal compared to hormonal male contraceptives given the difficulty with oral dosing of testosterone. The following sections highlight past and ongoing efforts to develop non-hormonal contraceptives for men.

Gossypol

The first extensively studied non-hormonal male contraception was gossypol. Gossypol is a large molecule purified from the seeds of a cotton plant grown in China. Gossypol was tested as a non-hormonal male contraceptive in clinical trials enrolling more than 8800 men in China in the 1970s and 1980s. In these studies, gossypol administration reduced both sperm production and sperm motility via an unknown mechanism. Most treated men developed azoospermia and Gossypol had a greater than 90% efficacy in pregnancy prevention. Unfortunately, side effects including hypokalemia and hypokalemic periodic paralysis occurred in about 1% of treated men. In addition, spermatogenesis did not fully recover in 10-20% of men. Despite significant efforts to chemically modify the structure of gossypol to reduce the risk of side effects, the study of Gossypol for non-hormonal male contraception has been largely abandoned.

Triptolide/Triptonide

A second naturally-derived male contraceptive compound studied in China was the herb *Trypterigium wilfordii*, the active compound of which is called triptolide. *Trypterigium* had been in traditional Chinese medicine for many centuries for the treatment of arthritis. Clinical study of patients treated with this compound showed that *Trypterigium* administration impaired sperm motility and decreased sperm counts. Unfortunately, as was the case with gossypol, several men experienced irreversible suppression of spermatogenesis and other side effects, causing the abandonment of work studying this compound as a reversible male contraceptive. Recently, a related compound, triptonide, has shown potent contraceptive properties in animal studies without the toxicities observed with triptolide. Further work with this compound will be of great interest.

Adjudin

The compound Adjudin was studied as a non-hormonal male contraceptive in animal studies in the early 2000s. The administration of Adjudin to rodents interferes with the ability of spermatids to adhere to Sertoli cells. Because of this, the spermatids undergo premature spermiation resulting in the production of non-functional spermatozoa that are incapable of fertilization. In rats, administration of 50 mg/kg of adjudin twice weekly induced 100% infertility after 5 weeks of treatment without changing serum gonadotropins or testosterone concentrations. Unfortunately, several animals experienced liver inflammation in a 29-day study at this dose. Follow-up work conjugated Adjudin to a FSHβ mutant, specifically targeting it to Sertoli cells, thereby reducing systemic exposure. Unfortunately, this approach proved prohibitively costly, and further study in either animals or humans of this conjugate was not undertaken.

EPPIN

EPPIN is a protein located on the surface of the sperm. EPPIN functions in liquefaction of the ejaculate; the absence of liquefaction severely impairs sperm motility. Initial immunization studies in male non-human primates demonstrated that a majority could be immunized against EPPIN. Notably, these males were mated and were unable to father pregnancies. Importantly, the animals re-gained fertility after

cessation of the injections. After this proof-of-principle immunization study, this research group has focused their work on developing small molecules that inhibit EPPIN binding to the protein semenogelin. A recent publication demonstrated that IV administration of the small molecule EP055, temporarily reduced sperm motility by 80% in male macaques. The group is now working on the development of potent, oral compounds in animal studies. Hopefully, continued work on this approach will result in a pill that can effectively reduce sperm motility for testing as a male contraceptive.

BRDT Inhibition

The bromodomain protein, BRDT, is required for meiosis. Intriguingly, men with mutations in the *Brdt* gene have infertility and semen analysis reveal abnormal sperm heads and poor motility. In 2012, a group showed that JQ1, a small molecule that potentially inhibited BRDT function, was shown to reversibly suppress fertility in a murine model. Unfortunately, JQ1 inhibits other bromodomain proteins, leading to toxicity. This group is performing structure-activity modeling of JQ1 in efforts to develop a BRDT specific inhibitor, retaining the contraceptive action while minimizing the potential for side effects.

Retinoic Acid Receptor Antagonists

It has been known since 1925 that vitamin-A (retinol) is essential for sperm production and male fertility. All of the effects of retinol appear to be mediated by retinoic acid. Retinoic acid functions via binding to a family of retinoic acid receptors (RARs), which serve to regulate gene expression. Gene knockout experiments have shown that mice with deletion of one of several of the RAR are sterile. Based on these observations, several groups are working on developing non-hormonal approaches to male contraception based on the blockade of retinoic acid function or biosynthesis.

One example of such a compound is BMS-189453, which was described in the early 2000s. This compound is an oral RAR pan-antagonist. Initial one-month studies of BMS-189453 at doses of 15, 60, or 240 mg/kg to rats lead to marked testicular degeneration and infertility, but also liver toxicity. A second group of investigators followed-up on these earlier studies, testing lower doses of BMS-18945, demonstrating efficacy at sperm suppression without the liver toxicity observed with larger doses. For example, mice treated

with 2.5-5 mg/kg for 4 weeks were completely sterile by 4 weeks of treatment with return to fertility 12 weeks after the cessation of treatment. A specific retinoic acid-alpha antagonist, YCT 529, appears to be effective as a contraceptive in rodents and larger species and may enter clinical testing soon.

Retinoic Acid Biosynthesis Inhibitors

Almost sixty years ago, the administration of WIN 18,446 was shown to dramatically suppress sperm production in men and was studied as the first non-hormonal male contraceptive in almost 100 men. Unfortunately, it was discovered that men taking WIN 18,446 had serious "disulfiram reactions" characterized by vomiting, sweating and palpitations when they drank alcohol while taking WIN 18,446. Because of these severe disulfiram reactions, further study of WIN 18,446 as a male contraceptive stopped. In 2011, it was shown that WIN 18,446 functioned via inhibition of testicular retinoic acid biosynthesis. It was further demonstrated that WIN 18,446 inhibited two enzymes called aldehyde dehydrogenase ALDH1A1 and ALDH1A2 that are the final step in retinoic acid production. Work in this area is now focused on the production of novel that specifically inhibit ALDH1A1 and 1A2 without causing disulfiram reactions, which are mediated by a similar enzyme ALDH2.

Gendarussa

An Indonesian traditional medicine called *Justicia gendarussa* has been reported to be used as traditional form of contraception by men in Papua New Guinea. The active ingredient is thought to be a flavonoid called gendarusin A. Some data on contraceptive efficacy for this compound has been reported in abstract form, but not published. In addition, the mechanism of action remains unclear. Therefore, additional information will be needed to determine whether this is a viable approach to developing a non-hormonal male contraceptive.

Vas Occlusion Methods

Several research groups have conducted research directed towards developing methods to reversibly plug the vas deferens since the 1970s. Reversible vas occlusion is an attractive approach to male contraception, as the initial vasal obstruction could provide long-

lasting contraception. Ideally, the man could later have the obstruction removed, and have his fertility restored. An Indian vas occlusion device called RISUG (reversible inhibition of sperm under guidance) has been studied in several clinical trials in men. The initial procedure is performed under ultrasound guidance. Specifically, a solution of styrene maleic anhydrate is injected into the vas deferens bilaterally, effectively occluding the vas and preventing the passage of sperm during ejaculation. Data from several small clinical trials of RISUG is available. Taken together, these studies demonstrate effective contraception over periods of up to one year in men. Unfortunately, no data from large-scale trials or demonstration of reversibility have been published.

A re-formulation of RISUG, called "Valsalgel™" in the US was tested as a contraceptive for one year in rabbits, and monkeys. After reversal, however, the sperm of the rabbits no longer had acrosomes, possibly due to inflammation in the vas. Therefore, as was the case with in the Indian studies, it remains unclear if RISUG is truly reversible. In similar work, Vas occlusion devices using medical-grade silicone and polyurethane were studied in China in the 1990s. However, these devices also experienced incomplete recovery of sperm parameters after attempted reversal. Newer work from China and the US with intravasal hydrogels, which may be more reversible, is showing promise and may be entering clinical trials soon.

Thermal Contraceptives

The application of heat to the testes can impair spermatogenesis and has been studied as a contraceptive in small studies. In one study of five men, the long-term use of specialized underwear that elevates the testes to near the outer inguinal ring lead to reversible suppression of sperm production and abnormal sperm. Additional testing of this approach with larger groups is warranted.

Conclusions

Contraception provision is essential for the prevention of unintended pregnancy. Given the limitations of currently available methods of contraception, there is a great deal of interest in the development of novel male contraceptive methods. Several non-hormonal approaches have been studied in mostly pre-clinical studies, but large-scale human studies to determine their safety and

efficacy are lacking. Additional research is required to meet the unmet need of male-driven methods of birth control.

Suggested reading

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