Review article :

Male contraceptive vaccines: Review article

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Abstract:

Contraceptive vaccines (CV) may provide viable and valuable alternatives to the presently available methods of contraception. The molecules that are being explored for CV development either target gamete production [luteinizinghormone-releasing hormone (LHRH)/GnRH, FSH], gamete function [sperm antigens and oocyte zona pellucida(ZP)], and gamete outcome (HCG). CV targeting gamete production have shown varied degrees of efficacy; however, they either affect sex steroids causing impotency and/or show only a partial rather than a complete effect in inhibiting gametogenesis.

Key words: Male contraceptive vaccines

Introduction

In the present day, birth control and family planning are of major concern. Besides the availability of the present methods of birth control, the population explosion and unwanted pregnancies continue to pose major health problem worldwide. However, the contraceptive options available to men are limited to vasectomy, condoms and early withdrawal, all of which present certain problems. The vasectomy is considered to be a permanent method of birth control because the surgery to reverse infertility has only a limited success rate. The latter two methods have failure rates even under perfect use. In order to check population explosion particularly in developing country like India, there is great need to develop a contraceptive method which will be effective, reversible, long lasting and easy to administer through the infrastructure of the developing nations.

A contractive vaccine (CV) has been proposed as a valuable alternative that can fulfill most, if not all of the properties of an ideal contractive. Since the developed and most of the developing countries have an infrastructure for mass immunization, the development of vaccines for contraception is an exciting proposition. The molecules that are being explored for CV development divided into three main categories.CV act on gamete production, gamete function and gamete outcome. CV targeting gamete production include anti-luteinizing hormone releasing hormone (LHRH) / GnRH vaccines ; Those targeting gamete function include anti- sperm and anti- oocyte zona pellucida (ZP) vaccines ; and those targeting gamete outcome include anti-HCG vaccines.[1] This article takes review on progress of various CV, their current status and future perspectives.

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Hormonal Contraceptive Vaccines:

Primary requirement for a molecule to be contraceptive vaccine include:

- Molecule should have specific role in the reproductive process.
- Its absence should not have any adverse effects other than impairing infertility.
- It should be easy and economically viable to produce on a large scale.

The potential target molecules are hormones involved in spermatogenesis which include LHRH, LH and FSH.

LHRH based vaccines :

LHRH vaccines conjugated to carrier proteins including bovine serum albumin (BSA), tetanus toxoid (TT), diphtheria toxoid (DT) and key hole limpet haemocyanin (kLH).[2] LHRH vaccine has been tested for its efficacy in blocking LH and FSH secretion in both the female and male of several species of animals. Both the vaccines have been highly effective in causing a significant reduction in testosterone production leading to a significant diminution in testicular and prostate weight.[3] Although the use of these LHRH conjugates as contraceptive vaccine for the human male has been mooted, they are currently been tested only for control of prostatic cancer. In patients with prostate cancer and benign prostatic hypertrophy (BPH), three injections of the modified LHRH vaccine conjugated to DT followed by two further doses at 6 weekly intervals apparently leads to production of anti – LHRH anti-bodies. This resulted in a reduction of FSH, LH, testosterone concentration as well as shrinkage of prostate size.

However the problems encountered with current vaccine formulation are as follows :

The vaccine formulation requires frequent boosters to maintain high anti body titres.

Repeat immunization over a protracted period with vaccine may not elicit the required response to maintain high titres of LHRH anti-body for prolonged periods. This is because the carrier proteins are potent immunogens and hence their antibodies remain in circulation for much longer time.[4] To overcome this problems of hyperimmunisation to the chosen carrier, Talwar's group preferred to immunize women initially with a combination of human chorionic gonadotrophin (HCG) βTT+HCGβDT followed by a booster at any one time with either of the conjugate alone.[5] It is unclear whether this strategy succeed in the human male.

LH Vaccines:

The studies with ovine LH vaccine show that the antibodies generated resulted in a marked reduction (90%) in serum testosterone concentrations after 8-16 weeks of immunization. The resultant azoospermia is due to 'arrest' in meiosis which is under the control of testicular testosterone.[6,7] However, immunized animals exhibited a marked reduction in testicular weight with a significant reduction in body weight, accompanied by noticeable muscle wastage and alopecia. The detrimental effects led to abandoning of further studies on the evaluation of ovine LH as a potential contraceptive vaccine for the male.

LH receptor vaccines:

Attempts to use the LH receptor, instead of LH, to obtain bio-effective antibodies have hitherto not met with complete success. The antibodies generated as a primary response were receptor binding agonistic antibodies leading to a marked increase (3-6 fold) in serum testosterone concentration instead of the expected fall. Moreover, a secondary response was

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seen leading to production of antibodies which were antagonistic. Because of the apparent hormone-mimicking activity of the first type of receptor antibody, serum testosterone concentrations in the immunized subjects were never reduced compared with normal values.[8]

FSH based vaccine:

An antibody to FSH or to FSH receptor leads marked inhibition in spermatogenesis as well as impairment in the spermiogenic process.[6,7] Though such a blockade resulted only in oligozoospermia, the quality of the spermatozoa produced was affected to a significant extent, leading to the establishment of infertility. The unique advantage of this approach is that neutralization of FSH does not have any effect on serum testosterone level and thus does affect libido. A pilot study carried out in five human male volunteers (Ovine FSH immunizations given on days 0, 20, 40 and 70 of the study) indicated that the vaccine in its current formulation and dosage was well tolerated and did not cause any immediate adverse effects. No significant immunopathological effects were recorded.[9] However, constraints in the availability of sufficient quantities of recombinant FSH, methods to sustain uniform effective response in all the immunized subjects and the need to use alternative methods of contraception until the required titres are reached, are the major deterrents for the practical application of this method.

FSH receptor base vaccine:

An FSH receptor protein fragment (1 – 134 amino acids) obtained by the recombinant route has been used to produce successful and effective antibody titres of prolonged bioefficacy (>300 days) after only two or three injections of the immunogen.[10]

Epididymal antigens:

Spermatozoa undergo a maturational process in the epididymis, where they are stored before ejaculation. Interference with epididymal function could be a useful approach to contraception. Within the epididymis, contraceptive effects could be mediated on the spermatozoa directly via the epididymal epithelium on epididymal fluid composition or on epididymal peritubular muscle.

Recently published in vitro studies have illustrated that TNF--$alpha$ produced by sertoli and germ cells into the microenvironment during spermatogenesis facilitates germ cell migration through blood testis barrier.[11] Molecules involved in sertoli-germ cell adherns dynamics in the seminiferous epithelium is also one of the areas of research.[12] Thus, all these aspects of epididymal function are being investigated as potential contraceptive targets and it is hoped that by interfering with the process of sperm maturation in the epididymis, an ideal contraceptive can be developed without interfering with the libido. However, none have thus far been translated into clinical studies.

Spermatic antigens:

A number of spermatozoa antigen have been investigated as immunological targets in animal models. Some of them with promising results are:

- Immunisation against one such antigen, PH-20, induced reversible infertility in all male guinea pigs treated with infertility in all male guinea pigs treated with infertility lasting longer than 1 year in some cases.[13] The identification of human proteins with similar roles raises the possibility for clinical studies in men.[14]

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- A cation channel specific for sperm motility has recently been identified and demonstrated to be specifically expressed on the sperm tail, targeted disruption of which reduced spermatozoal motility and abolished the ability of sperm to penetrate the zona pellucida and fertilize the egg but had no other apparent effect.[15]
- LDH4 is an isoenzyme of lactate dehydr-ogenase, a glycolytic enzyme that is found only in male germ cells and detailed studies have been carried out on its structure and function.

Other antigens which are being tested in experimental animals include RSA-1 human SP17, Tcle-1, and SP10. However, none of the studies have reached a stage where it can be inferred that a particular antigen can be the candidate for use as a contraceptive vaccines.

Conclusion and future prospects:

In men LHRH &FSH have been suggested as possible targets for immunocontraception, if azoospermia is the desired goal LHRH based vaccines may be the candidate vaccine of the choice. The problem with this vaccine is that the exogenous testosterone administration will be required for maintenance of androgenicity.

Genetic engineering using murine models has already revealed some intriguing non –hormonal targets. The most recent work has been done to develop vaccines aimed at GnRH-1DNA[16.] Thus development of a viable hormonally based contraceptive vaccine for the male is possible.

Drawbacks for CV include need for periodic injection, variability in immune response triggering autoimmune disease and perhaps anaphylactic shock. So immunological approach to contraception is not without problems.

Advanced research is needed to determine the proper choice of carrier protein, adjuvant and immunization protocol which would entail a booster only once in 6-12 months.

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