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Calcium Channel Blocker (Quinidine) as a New Approach of Male Contraception: A Review

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Abstract
The intentional avoidance of conception via the using a various strategy, sexual practices, chemicals, drugs or surgical method. A successful contraception was permitting a physical relationship between partners without worrying about an unwanted pregnancy and makes sure a freedom to have children when in demand. The purpose is to attain contraception with a highest confidentiality and a minimum cost and side effects. Even though, the intention to finding a new approach of male contraceptives through targeting ion channels was disturbed by lacking the most molecular basis of channels to effect on sperm function. Recently, there is developing of a new approach push of male contraception, based on targeting specific processes in sperm development, maturation, and function by using quinidine as a one of calcium channel blocker. Consequently depending on previous findings and researches on sperm-specific Ca^{2+} channels, as new non-hormonal drug targets for male contraception.
Keywords: Catsper, Male Fertilely, Contraception, Ca^{2+} Channel Blockers

1. Background of Male Contraception

Clear evidence observed that women instead of men are paying interestingly for birth control. From many years ago, in addition no attention has been given to men as women. For this reason in the market, many of the contraceptive methods are female oriented (Nabi et al, 2014). New male methods of contraception have not been available. The sperm channel approach based on inhibition of calcium entry to sperm and, as a result, shows its effected on testicular function and spermatogenesis, which investigated for several decades. This approach achieves enough suppression of spermatogenesis to succeed contraception in most men, but not all; the basis for men to respond to this way still unclear. On the other hand, the establishment of non-hormonal approach depended on sympathize specific processes in sperm development, maturation, and function. A variety of targets in animal models has been well-known. This approach, however, still under in the preclinical trial at present. As a result, fundamentally for considering if it is safe have no harmful effects, should be efficient and reversible with minimum cost, then the new method of male contraception can be developed.

2. Introduction

Clear Contraception defined as prevention of pregnancy by using different procedures such as chemical drugs, surgical operations, and sexual plan. Thus, any means can conceive contraceptive whose essential objective to avoid conception. The most contraceptive methods, in which the scientists have been trying in the past 40 years, to develop favorable male contraceptives beyond traditional contraception options, are condoms and vasectomies. Condoms for both (male and female) provide advantages with contraception and protect the partners from sexually transmitted diseases (Jain, Muralidhar, 2011).

2.1 The purposes of contraception

2.1.1 Protection against unwanted pregnancy

Growing number of women and men of reproductive age wish to regulate their fertility and have fewer children .Otherwise, contraception is convenient and used consistently by women wanting to avoid pregnancy, maternal deaths would decline by an estimated 25–35% (Lule, Singh, Chowdhury, 2007; Organization, 2010).

2.1.2 Need for Protection against Sexually Transmitted Diseases

The vagina offers a large mucosal surface exposed to the partner's sexual secretions and a more encouraging environment for microbial growth than the penile surface in men. Therefore, biologically women are considered to be more susceptible to STIs than men. The ability of STIs and HIV/AIDS transmission from an infected man to the uninfected woman are higher than the reverse (Washington, Cates, Wasserheit, 1991).Since the infected semen stays in the vagina for a short time, in fact a man can infect the woman more. Also, semen contains a

higher concentration of virus than the woman's sexual secretions. Thus, men are twice more susceptible as transmitters of STIs than women.

2.1.3 Socio-economic and cultural factors

The occurrence of pregnancy in adolescent varies depended on countries and socioeconomic levels. In developed countries , the fertility rates in women aged 15-19 years is 30 /1000 with lowest rates under 20/1000 in teen-aged women found in parts of Europe and Eastern Asia (Organization, 1998; Paxman, Rizo, Brown, Benson, 1993).

2.2 Methods of male Contraception

2.2.1 Male withdrawal

Involved withdrawal of the penis from the vagina just before ejaculation, thus preventing semen from entering the woman. This is perhaps the oldest contraceptive method known to man, but it depends on the cooperation of the male partner. Man needs enough self-control, both emotionally and physically for this method to succeed.

2.2.2 Male Condom

The first designated of a condom were in the 16th century. It prevents semen (sperms) from entering the woman. The method is 95% effective if used correctly. It can be utilized by all age groups, safely. No prior medical examination required and is easily available without a prescription. Because of their safety, condoms are the favored way in both male and female for contraception.

2.2.3 Injecting plugs into the vas deference

One approach studied was injecting plugs into the vasa deferentia caused vas segments occluded by the standard procedure of medical polyurethane-vas occlusion (Chen, Gu, Liang, Shen, Zou, 1996). This method had been applied widely in China. However, the amount of published clinical data on this method is even more limited than hormonal alternatives.

2.2.4 Heat treatment

This approach depended on heating, induced apoptosis of germ cell. The heat treatment designed for testing in monkeys and has proven to be useful (Liu 2010), by locally warming monkey testes in water at 43°C for continuous two days; the sperm count in the semen could up to 80 % after 28 days (Liu 2010). At this point, however, this method is still limited to the animal trial stage. In this method, testis are heated until, block sperm formation (spermatogenesis) for 45 minutes at 47 °C just below the threshold of pain. This method is not an attractive technique because of severe side effects (Wang, Swerdloff, 2010).

2.2.5 Immuno-contraceptive vaccines

It has been, developed in animal trials targeting some sperm surface antigens, such as PH-20 (Hardy, Clydesdale, Mobbs, Pekin, Lloyd, Sweet, Shellam, Lawson, 2004). The development of PH-20 as a contraceptive depended on the generation of appropriate sources of antigen and delivery mechanisms (Holland, Andrews, Clarke, Walton, Hinds, 1996) and SP-10 (Aitken, 2002).Further research on multi-epitome vaccines and sperm-specific antigens would provide an efficacious and viable to contraception (Naz, 2009).

2.2.6 Herbal Medicines

Herbal contraceptives can help the partner to control their fertility without interviewing a physician. Herbal contraceptives have fewer side effects and are readily available. They protect the privacy and can increase the number of couples to practice family planning. Gossypol, derived from plants and traditional Chinese medicine, is a natural constituent of cottonseed oil which used for cooking in China. *Tripterygium wilfordii* is a traditional Chinese medicine, proved to have potent anti-fertility effects (D'Cruz, Vaithinathan, Jubendradass, Mathur, 2010).Among these compounds, only gossypol had been intensively studied and then abandoned for contraceptive use, due to its slow recovery pattern and irreversible effect (Waites, Wang, Griffin, 1998).

2.2.7 Hormonal male contraceptives

It can suppress testosterone production in the testis and impaired spermatogenesis (Grimes, Lopez, Gallo, Halpern, Nanda, Schulz, 2007).In addition, the scientists have confirmed the suppression of spermatogenesis by exogenous multiple hormones, similar to female contraceptives (Gu, Liang, Wu, Liu, Song, Cheng, Bo, Xiong, Wang, Liu, 2009).Additionally, this method has unwanted side effects, especially hormonal imponderables including a decreased in the production of testosterone that leads to loss of libido, which could not neglected. Therefore, until now, there has been no available hormonal male contraceptive on the market, and it may take time before this information becomes available. Development of a male contraceptive targeting the hormonal control of spermatogenesis, consisting of a progestin and testosterone, is the most developed pharmaceutical option at this time. Testosterone administered in combination with other hormones has shown considerable promise in clinical trials, and they are currently at the front position of research and development (Cheng, Mruk, 2010).The approach is to down-regulate pituitary release of LH and FSH resulting in decreased.

Recent studies established patch-clamp technique on whole sperm for identification of functional ion channels and has opened up a new class of targets to inactivate sperm functions (Kirichok, Navarro, Clapham, 2006). In 2001, one approach basis for blocking sperm motility and sperm hyper-activation specially has first determined on a novel sperm transmembrane calcium channels called CatSper (Ren, Navarro, Perez, Jackson,

Hsu, Shi, Tilly, Clapham, 2001). These transmembrane proteins enhanced Ca^{2+} influx into the sperm tail through a bicarbonate-activated, voltage-sensitive channel. The increasing of intracellular calcium mediated by the CatSpers is directly essential for the increase in flagellar beat frequency that characterizes sperm hyperactivation .So that, CatSpers are important for fertility, and CatSper-knockout animals are infertile (Ren, Xia, 2010).Therefore, CatSpers are the promising targets for male contraceptive development, on the other hand the relative potent Slo3 blocker quinidine is a wide spectrum blocker of slo3, and it has been reported to have ability of inhibiting Catsper (Zeng, Yang, Kim, Lingle, Xia, 2011) .

2.2.8 Catsper blocker a new approach to male Contraception

Ion channels have a fundamental role in involvement sperm fertility processes: maturation, capacitation and acrosome reaction. Furthermore the blocking of calcium channels by pharmacological inhibitors or compounds from isolated from plant were reported as one of promising mechanisms of future male contraceptives (Driák, Svandová, 2012). though, the attempting for developing the male contraceptives by targeting ion channels has largely been interfere by lacking of molecular recognition information of the channels to be existed in sperm, such lacking these proteins function at the final stages of sperm maturation make them to be a model targets for contraceptive development, then the studies for both vaccine and pharmaceutical development have been confirmed (Zheng, Wang, Li, Zeng, 2013). The recent founding of patch-clamp methodology in whole sperm has been essential to identified the function of ion channels and has opened up a new approach of targets to inactivate sperm (Kirichok *et al.*, 2006). A voltage-gated calcium channel was restricted to sperm is constructed using four gene products: CatSper (sperm-associated action channel) 1–4.Three other gene products are associated with the CatSper complex, this channel is regulated by pH, prostaglandin, and the progesterone produced by cumulus cells in the egg of human oviduct (Kirichok, Lishko, 2011; Strünker, Goodwin, Brenker, Kashikar, Weyand, Seifert, Kaupp, 2011).

2.2.9 Quinidine targeting Ca^{2+} channels (Catsper blocker)

Quinine is a rapidly antimalrial agent, gradually has been concerned in reproductive toxicity (Farombi, Ekor, Adedara, Tonwe, Ojujoh, Oyeyemi, 2012). Some studies established that quinine is a testicular toxicant (Osinubi, Ajala, Noronha, Okanlawon, 2006). The toxic effects of this anti-malarial alkaloid on human and animal sperms have been observed by biomedical researchers applied in vivo and in vitro.The inhibitory effect of both quinine and chloroquine on sperm metabolism (measured by production of lactic acid and CO_2) and motility have been reported (Trifunac, Bernstein, 1982), moreover in vitro study showed the spermicidal activity of quinine after 20 sec of incubation sperms with this alkaloid resulted about 100% of human spermatozoa were immobilized (Garg, Doncel, Chabra, Upadhyay, Talwar, 1994).Another in vivo study in rats observed the toxic effect of short term administration of quinine on the seminiferous tubules , determined that disturbance of spermatogenesis (Osinubi, Akinlua, Agbaje, Noronha, Okanlawon, 2004) and degenerative histological changes in the germinal epithelium as well as statistically significant decrease in sperm count, sperm activity and percentage normal morphology (Nwangwa, Igweh, Uzuegbu, Adegor, 2007) .This seems to be participate by the report by Abayomi etal.(1992) that chloroquine treatment of rats eventually would lead to infertility by resulting in late germ cell developmental with depletion of spermatids (Abayomi O, 1992).This suggested the requirement for the quinine to occupied a place as a male contraceptive agent in humans (Osinubi *et al.*, 2004). Therefore we concluded from this study that the proposition based on the findings in studies in non-human subjects that short-term use of agent to treat malaria has a significant anti-spermatogenic and anti-fertility or contraception.

From molecular side ,quinine known as a blocker of a large number of different K^+ channels, a number of voltage-dependent K+ channels, blockade of voltage-dependent channels in many such cases favored by depolarization (Fedida, 1997; Snyders, Knoth, Roberds, Tamkun, 1992; Yeola, Rich, Uebele, Tamkun, Snyders, 1996).On the other hand , earlier studies on β-cells confirmed that quinine has been used as a blocker of Ca^{2+} activated K+ channel (Atwater, Dawson, Ribalet, Rojas, 1979), also inhibit Ca^{2+} activated and ATP-regulated K+ channels (Bokvist, Rorsman, Smith, 1990),the effects of quinine on the Ca^{2+} activated K+ channel had a rapid onset and were fully reversible (Bokvist *et al.*, 1990).Advanced studies showed that CatSper is the only mammalian sperm calcium channel which can be detected directly by electrophysiological method and whose function has been supported by gene manipulation (Kirichok *et al.*, 2006; Ren *et al.*, 2001),some of Catsper properties make it an likeable target for male contraceptive development(Carlson, Burnett, del Camino, Quill, Hille, Chong, Moran, Babcock, 2009; Navarro, Kirichok, Chung, Clapham, 2008).The channel protein have an important role in male fertility, supposed the antibody or drug that blocks its activity suppress and impair fertilization .Additionally ,the expression of Catsper have to be limited to spermatogenic cells and mature sperm, excluding any off-target effects in other parts of the body (Ren *et al.*, 2001), subsequent to ejaculation these channel proteins remain available, inspiring a contraceptive agent administered orally could arrive at the channels on the sperm surface. Furthermore, as Catsper channels only occupied in mature sperm, the reversible recovery of such an antibody or drug could be achieved if it is administered only even as the partner is sexually active.

The option for designing a male, non-hormonal contraceptive , more consideration should be take

place including efficacy, safety, reversibility, and ease of delivery (Nass, Strauss, 2004), The vital properties of CatSper channel on sperm (for review see Navarro et al (Navarro *et al.*, 2008) make this attractive proteins target for contraceptive development. First, the required role of CatSper channel proteins in male fertility indicates that a CatSper channel blocker should effectively prevent fertilization. Second, CatSper channel proteins are found only in sperm and spermatogenic cells, indicating that a CatSper-specific blocking drug would have no channel-related actions elsewhere in the body. Third, the CatSper proteins apparently function only in mature sperm, indicating that a CatSper-blocking drug could be delivered only during periods of sexual activity to acutely prevent sperm from reaching and entering the egg. Such actions should be entirely reversible when delivery of drug ceases. By limiting treatment to periods of sexual activity, any cumulative off-target actions would be minimized. Fourth, the CatSper channel proteins in the surface membranes of sperm remain accessible after ejaculated sperm have left the protected environments of the testis and epididymis, indicating that oral delivery of small water-soluble drug could reach CatSper channels through transfer from serum to reproductive fluids. Oral delivery shortly before sexual activity should be a highly-acceptable treatment, with high compliance.

3. Conclusion

There is a universal demanding for an ideal method of contraception. As well as in countries especially in china because the policy to having one child or at least two in some special cases, there is an urgent requirement for contraceptive methods, which can based on blocking of Ca^{2+} entry into the sperm through using specific Ca^{2+} channel blocker , such as quinidine and thus on testicular function and sperms behavior can realize adequate suppression of sperms used for effective contraception in most male. An additional work is required on future study to clarify the mechanism of QD and find out the outlook of QD as a male contraception.

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Ion channels assessed by electrophysiology in human and mouse sperm. Adapted from Lishko et al.(Lishko,

Kirichok, Ren, Navarro, Chung, Clapham, 20

Channel/ Species	**Gene**	**Ion selectivity**	**Location**	**Role in Sperm Physiology, including sperm specificity**	**Endogenous Regulators**	**Knockout phenotype**	**Pharmacological antagonists and concentrations**	**Pharmacological agonists and concentrations**
Catsper (Human) (Mouse)	Catsper1 Catsper2 Catsper3 Catsper4 Catsperβ CatsperγCatsperδ	Ca^{2+}	Principle piece	Ca^{2+} influx resulting in sperm hyperactivation	Progesterone PGE1(b) pHi Egg coat proteins, albumin	Infertile poor motility	NNC55-0396 (1-10µm) Miberfradil (30µm) MDL12330A (100µm)	PGE1(500µm) Progesterone (500mM) Undecanal (50µm) Bourgoenal (50µm) Helional (100µm) Cyclamal (10µm) 8-Br-cGMP (5mM) (-)Menthol (3mM)
Ksper (Mouse)	Slo3	K^{+}	Principle piece	Regulation of membrane potential, sperm specific	pHi, PIP2, LRCC52	Infertility Hairpin Morphology Poor motility	Quinine (500µm) Clofilium (50µm) EIPA (50µm) Miberfradil (5µm)	AP(4mM) NH4Cl(1mM)
Hv1 (Human) (Mouse)	Hven1	H^{+}	Principle piece	Removal of inracellualr H+ from flagellum, alkalises cytoplasm, Not sperm specific	pHi , Vm , removal of zinc, anandamide	Not in mouse Hv1-/- are fertile	Not investigated	Oleic acid (100µM) Anandamide (>3µm)
1ATP (mouse)	P2rx2	Na^{+}, K^{+},Ca^{2+}	Midpiece	Widespread		P2rx2-/- Mice Are fertile	Not investigated	ATP(100µM)
CaCC (Human)	Anol	Cl^{-}	Unknown	Cl- efflux resulting in AR	Ca^{2+}	Anol-/- Lethal at birth in mouse	Not investigated	NFA(10µm) DIDS(20µM) TMEM16A(10µM)

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