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Efforts to Generate a Male Contraception Just by Prevention of Sperm Motility Acquirement in Epididymis Without Influencing the Physiology of Spermatogenesis: Yet Still a Little Far Goal

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ABSTRACT

In view of the world population escalating at an alarming rate anticipated population will reach 9.8 billion by 2050. In contrast to female contraceptive measures male contraceptive methods are relatively negligible .Maximum researchers have concentrated on generation of male contraceptive methods by trying to modulate hormones but had to abandon this strategy as the pharmaceutical companies were not happy in view of marked adverse actions. Maximum nonhormonal strategies in research concentrate on spermatogenesis repression or reversible physical barriers. Sperm motility represents one of the maximum significant markers of semen quality as it is necessary for sperm motion appropriately in the female reproductive tract for it to arrive intricately towards the egg as well as fertilize it.

The group of Vijayraghavan S, et al. have been concentrating on generation of a male contraceptive by utilization of targeting sperm motility at epididymal level by extensively studying the regulation of flaggelar protein motion by various subunits like Protein Phosphatase 1 (PP1), Protein Phosphatase Inhibitor-2 (PPPIR2), its phosphorylation by Glycogen Synthase Kinase-3 (GSK3), A kinase anchor protein 4(AKAP4). Recently they attempted to generate a bioportide that could simulate binding of the anchor protein AKAP4 that had been earlier revealed as a PPγ2 interactor in human sperm,that are implicated in sperm motility .Unfortunately that did not abolish sperm motility completely .This seemed to be surprising as PP1/ PPPIR2crosstalk seems to be central in regulation of sperm motility. Thus Silva et al., pointed that evaluation of the probable part of PPPIR7 as well as PPPIR11 in the manipulation of sperm motility in men might be the aim of future studies that needs to be continued to get more insight in this field.

Keywords:

Male contraception, Biopeptides, Protein Phosphatase Inhibitor-2 (PPPIR2), Protein Phosphatase-1 (PP1), AKAP4

Introduction

In view of the world population escalating at an alarming rate-population has been anticipated to reach 9.8 billion by 2050 [1]. In contrast to female contraceptive measures male contraceptive methods are relatively negligible in addition to being underused [2]. Maximum researchers have concentrated on generation of male contraceptive methods by trying to modulate hormones [3]. Nevertheless, this has been given up by the pharmaceutical companies in view of marked adverse actions[4]. Maximum nonhormonal strategies in research concentrate on spermatogenesis repression or reversible physical barriers [2]. Sperm motility represents one of the maximum significant markers of semen quality as it is necessary for sperm motion appropriately in the female reproductive tract for it to arrive intricately towards the egg as well as fertilize it. Although over decades spent on getting insight into the mode by which acquisition of motility occurs in sperms at the time when they pass through the epididymis are still not appropriately clear. Nevertheless, lot of proof is there that the morphological integrity of the flagellum of the sperm, its capacity to generate energy that can provide adequate fuel for the flagellar movements, besides the activation or hampering of particular signaling pathways in addition to protein post-translational modifications are the crucial prior needs for sperm to achieve motility.Here we did a mini review to see what possible advances have been tried to attain a male contraceptive by targeting sperms at the epidymal level.

We did a review with utilization of search engines like Pubmed, Google Scholar with the utilization of MeSH terms like male contraception; sperm motility; sperm structure; flagellar structure;energy utilization; protein phosphatase1; protein phosphatase inhibitor2; GSK3; PP1γ2; CPP;bioportide from 1990's till 2021.

Structure of sperm flagellum

The sperm flagellum is made up of nine double microtubules that surround 2 central singlet microtubules that develop a 9 ± 2 structure known as axoneme that is correlated with radial spokes along with dynein arms. Every doublet microtubule possesses a greater amount of acetylated tubulin, whose

framework alteration lets dynamic bending along with twisting of doublet microtubules. The sliding motion of microtubules is secondary to the stimulation of ATPases of the dynein arms that convert a chemical energy signal of ATP into mechanical or physical electrical signal. Huge levels of Adenosine Tri-Phosphate (ATP) are needed for facilitation of sperm motion.

Fuel generation for sperm motility

Despite the posit that mitochondrial oxidative phosphorylation might be the major origin site for ATP generation in sperm, almost presently it was illustrated that totally glycolysis is the advantageous metabolic pathway which generates fuel needed for sperms to move.Mammalian sperms possess clearcut isoenzymes implicated in glycolysis. Of these Glyceraldehyde-3 Phosphate Dehydrogenase-S (GAPDS) was observed to have a key part in sperm glycolysis.Targeted removal of GAPDS (GAPDS-/-) mice caused a blockade of glycolysis with a 4 times collection of the substrate glyceraldehyde-3 phosphate in contrast to wild type mice .GAPDS-/- mice revealed normal sperm count, morphology in addition to testis weight histology, although they were infertile, secondary to significant abnormalities in sperm motility [5].

Regulation of sperm motility

On activation of motility, the particular actions of enzymes in the glycolysis pathway escalate that is followed by an enhancement of ATP generation.This sperm glycolytic pathway is regulated by male germline- particular isoenzymes that originate from genes or transcripts undergoing alternative splicing.An enhancement of cAMP amounts in addition to Protein Kinase A(PKA) stimulation probably starts motility in epididymal sperm, possibly secondary to alteration in protein phosphorylation. Specifically, a significant process that controls achievement of sperm motility appears to be under the regulation of sperm phospho protein phosphatase-1(PP1) (a serine/threonine phosphatase)action.This enzymes activity is great in the caput epididymis, where sperms are immotile; but this enzyme is inactive in the cauda epididymis, where the sperms have gained motility.The catalytic action of PP1 in mammals gets basically controlled by Protein Phosphatase Inhibitor-2 (PPPIR2) with PPPIR2 getting phosphorylated by Glycogen Synthase Kinase-3 (GSK3), PP1 is active along with sperms being immotile (caput epididymis) at a time when PP1 is bound to PPPIR2, thus is inactive while sperms are motile (cauda epididymis) [6].

Role of CPP/bioportides in male contraception generation

Recently Silva et al. [7], conducted an in vitro study for analyzing the influence of competitive bioportides [used in Cell Penetrating Peptide (CPP) technology] on PP1 activity in addition to human sperm motility with the idea of their proper utilization as newer male contraceptives that target the post testicular sperm maturation along with achieving the motility without any interference in spermatogenesis. In mammals PP1 gets encoded by 3 separate genes that generates PP1α, PP1β as well as PP1γisoforms. Following transcription, PP1γ goes via tissue- particular, from which a ubiquitous isoform PP1γ 1 along with a testis in addition to sperm particular isoform PP1γ2 that exists in the posterior as well as equatorial head area in addition to the total flagellum [8]. The molecular variation among these 2 PP1γ isoform is located in the carboxyl terminus (C terminal) [9]. The control of PP1 catalytic isoforms gets modulated by generation of holoenzymes with regulatory interactors of PP1 (RRIPPOs), previously known as PP1-interacting proteins[10]. They generated a Peptides mimetic of the PP1 binding motif of human A kinase anchor protein 4 (AKAP4) that represents a sperm-particular anchor protein that had been earlier revealed as a PPγ2 interactor in human sperm that are implicated in motility control, the PP1 binding motif of human PPPIR2 in addition to the unique 22-amino acid C-terminus of PP1γ2 that is a sperm- particular isoform believed to be the one that holds the maximum responsibility for the action of PP1 in the sperms of the mammals. Peptides were made to be covalently attached to a CPP that was inert in nature to generate bioportide fabrications with the main aim of interfering with the PP1 crosstalk in the spermatozoa that was intact.Thus all bioportides had the capacity to get into the sperm cell in vitro in addition to manage intra cellular collection without influencing the vitality of the sperm.Conversely, there was a significant impact on the progressive motions with the most influential outcomes on utilization of MSS1 that represents a bioportide which has been perfected with decreased size in addition to escalated potency of action that had been fashioned with the idea of enhancement o feffect of AKAP4-BM that had the capacity to result in significant reduction in the quantity of A kinase anchor protein 4 (AKAP4) protein that is bound to PP1γ2, along with the peptide simulating the unique 22-amino acid C-terminus of PP1γ2, that is attached with a CPP. Nevertheless, sperm motility did not get totally ameliorated by these bioportide fabrications. Thus Silva et al. [7], suggested that the combination of utilization of bioportides that were targeting the RVxF- binding area (MSS1) along with the bioportide simulating the unique 22-amino acid C-terminus of PP1γ2 might probably cause a complete finishing of the sperm motility. PPPIR2 represents a markedly intrinsically disarrayed protein that achieves a definite structure only on correlation with PP1 [10]. PPPIR2 possesses 2 degenerated RVxF motif's [11]. In mammalian sperms PP1γ2 seems to be the only molecule implicated for PP1 activity [12] as well as inhibition of PP1 by phosphatase inhibitors (Calyculin A as well as okadaic acid) stimulate caput sperm motility [12]. Despite such posit, might be right in the hypothetical sense, it would have been better to evaluate in this study instead of asking that it be exhibited by other future studies.

Conclusions

A significant observation of this study might open the way for more evaluation in this field is the finding that in vitro interference of PP1γ2/PPPIR2 crosstalk could not achieve total inhibition of sperm motility, following 2h of incubation with PPPIR2-BM bioportides, 19% ± 7.2% of bovine sperm still continue to be progressively motile. This appears astonishing as it has been pointed that PPPIR2 activity is central in regulation of PP1 activity in mammalian sperms. Actually it has been illustrated in the mouse that PP1γ2, catalytic activity gets regulated by 3 separate protein phosphatase inhibitors: PPPIR2, PPPIR11, along with PPPIR7 [13]. Binding of 13, PPPIR11, along with PPPIR7 to PP1γ2 alters during the sperm transiting via the epididymis. In caudal sperms, all the 3

inhibitors are bound to PP1γ2 that makes it inactive, whereas in the caput sperm phosphorylation of PPPIR11 avoids the binding of PPPIR7 to PP1γ2 that is thus catalytically active. Depending on these outcomes of Silva et al. [7], evaluation of the probable part of PPPIR7 as well as PPPIR11 in the manipulation of sperm motility in men might be the aim of future studies that need to be continued to get more insight in this field.

The study performed by Silva et al. [7], throws some light on the signaling events which control sperm motility, but still certain unanswered queries need to get tackled in future studies [see figure1]. It appears too early to talk about the clinical applications of bioportides as male contraceptives in view of their inherent pharmacodynamic as well as pharmacokinetic characteristic that the authors themselves agreed upon [14].

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