CYCLODEXTRIN NEWS
VOLUME 29. No. 1. JANUARY 2015 ISSN 0951-256X

CDs in Artificial Fertilization of Animals

Introduction

Artificial insemination of farm animals is very common in today's animal husbandry in the developed world, especially for breeding dairy cattle (75% of all inseminations) and swine (up to 85% of all inseminations). It is used for breeding buffaloes, sheep, goats, horses, dogs and a variety of laboratory animals as well. It allows a male to inseminate a much larger number of females and to use the genetic material from males separated by distance or time, to control the paternity of offspring, to overcome physical breeding difficulties, to synchronize births, to avoid injury incurred during natural mating and to avoid the need to keep a male in small herds [1].

Semen is collected, diluted, then cooled or frozen. To allow the sperm to remain viable during and after it is frozen, the semen is mixed with a solution containing various ingredients. Glycerol removes water from the sperms and thus prevents the formation of ice crystals during freezing. Sodium citrate, fructose and egg yolk are also typical cryoprotectants. A diluent is used to allow the semen from a donor to impregnate more females. Antibiotics, such as penicillin, streptomycin, are sometimes added to the sperm to control some bacterial venereal diseases. Before the actual insemination, estrus may be induced through the use of progestogen and Prostaglandin F2α.

Cyclodextrins can not only improve the pharmacological properties of the antibiotics, hormones and prostaglandins but can modify the cell membrane via the interaction with cholesterol. Such modification plays important role both in the freezing-thawing process and fertilization.

Mechanism of fertilization

The schematic structure of the sperm cells can be seen in Fig. 1. The head of the cell is covered by acrosome, which helps making way for the sperm cell through the jelly shell of the egg (zona pellucida) to get to the cell membrane of the egg/oocyte, where the fertilization takes place (Fig. 2). The first step is the capacitation, which involves the destabilization of the acrosomal sperm head membrane allowing greater binding between sperm and oocyte. This change is facilitated by the removal of steroids (e.g. cholesterol) and non-covalently bound epididymal/seminal glycoproteins. This happens normally in uterin by secreting cholesterol-binding albumin and other enzymes. The next step is the acrosome reaction, which means enzymatic hydrolysis of the glycoproteins, the main constituents of the jelly shell of the egg.

The acrosomal reaction does not begin until the sperm comes into contact with the oocyte's zona pellucida. The fertilization starts when spermatozoa binds to the extracellular matrix coating of the oocyte. A specific sugar sequence (sialyl-LewisX) helps in targeting [2]. Upon coming into contact with the zona pellucida, the acrosomal enzymes begin to dissolve and the actin filament comes into contact with the zona. Once the two meet, a calcium influx occurs, causing a signaling cascade [1]. In this complicated process the lipid raft protein caveolin-1 also plays a role [3].

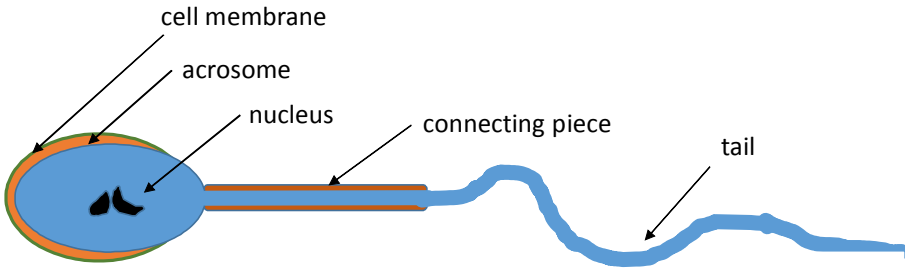

Figure 1: The schematic structure of sperm cell

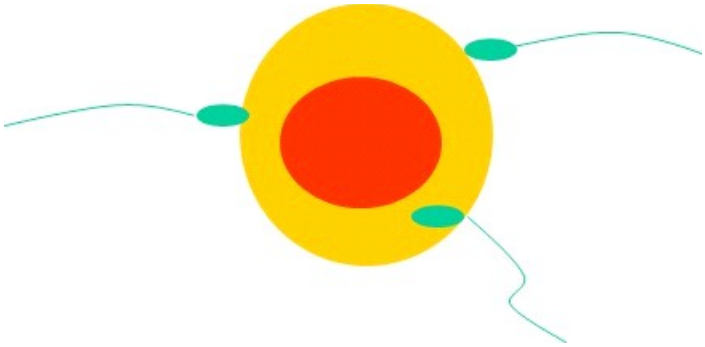

Figure 2: The process of fertilization: the maturated (capacitated) sperms arrive to the egg, bind to zona pellucida (the outer glycoprotein layer of the oocytes/eggs surrounding the plasma membrane), the fastest sperm penetrates the zona pellucida by the acrosome reaction (enzyme reactions enabling the sperm to break the membrane of the egg) and by the zona reaction the fusion of the membranes of the two cells occurs making possible the fertilization

Effect of CDs on the membrane of sperm cells and eggs

Membrane raft of eggs is involved in fertilization. Cholesterol removal by using methyl BCD (MeBCD) induced a decrease of the fertilization rate and index of mice. Cholesterol repletion recovered the fertilization ability of cholesterol-depleted oocytes, indicating reversibility of these effects [4]. Raft disruption by cholesterol depletion disturbed the subcellular localization of the signal molecule c-Src kinase playing an important role in the fertilization [5].

While cholesterol removal of oocytes is detrimental that of the sperm cells might have beneficial effects.

In protein-free medium (Krebs-Ringer bicarbonate medium) no fertilization of mouse eggs was observed *in vitro*, however, fertilization occured when spermatozoa were preincubated with MeBCD and in a smaller extent with HPBCD (41% vs. 14% at 0.75 mM concentration). When 4 mg/mL bovine serum albumin (BSA) was present 66% fertilization rate was obtained. Destabilization of the acrosome membrane via cholesterol efflux is the first step of capacitation of sperms. After incubation of mouse spermatozoa for 90 min in 0.75 mM MeBCD, the cholesterol content of the spermatozoa was significantly lower than that of the control (2.3 vs. 4.1 nmol unesterified cholesterol/10^7 sperm). The proportion of acrosome-reacted spermatozoa, however, was not different between MeBCD treatment and the control. Therefore, MeBCD increased capacitation rather than the acrosome reaction of spermatozoa [6]. Similar results were obtained for boar spermatozoa [7], rabbit [8] and dromedary camel [9].

Pre-incubation of bovine sperm with MeBCD affected viability and capacitation status of the sperm and promoted also fertilization *in vitro*. Embryos derived from oocytes fertilized with sperm pre-incubated with MeBCD developed normally [10].

In other experiments, compared to the non-MeBCD-treated control, MeBCD treatment increased the percentage of acrosome-reacted pig spermatozoa at thawing and 2 h after incubation in fertilization medium ($P < 0.01$). Treatment with MeBCD also increased sperm-penetration rate, number of spermatozoa in oocytes, and fertilization efficiency [11].

MeBCD improved the fertilizing ability of frozen/thawed C57BL/6 sperm (the fertilization rate for frozen/thawed sperm of this strain of genetically engineered mice is poor). The embryos with frozen/thawed sperm showed good developmental potential, and the offsprings had normal fertility. The efflux of cholesterol from frozen/thawed sperm was increased by MeBCD in a dose-dependent manner and occurred much earlier and to a greater extent than with bovine serum albumin [12]. Using MeBCD during sperm preincubation enhanced fertility of frozen/thawed C57BL/6 mouse sperm [13,14]. A new thawing method was developed that involves selective collection of motile sperm and a preincubation medium containing also MeBCD that enhances capacitation [15].

To become fertilization competent, mammalian spermatozoa undergo changes in the female reproductive tract termed capacitation. Capacitation is associated with an increase in proline-directed phosphorylation linked to cholesterol efflux in the sperm [16]. Cholesterol efflux was achieved by bovine serum albumin (BSA) or HPBCD in these experiments with mouse sperms. Fertilization stimulated tyrosine phosphorylation of signaling proteins of eggs in *Xenopus* [17]. Pretreatment of eggs with MeBCD led to a decrease in cholesterol and sperm-induced tyrosine phosphorylation in the membrane resulting in inhibition of sperm-induced Ca^{2+} efflux and first cell division [18]. The fertilizing state was correlated with an increase of protein tyrosine phosphorylation and a decrease of sperm cholesterol content. Inhibition of either the increase in tyrosine phosphorylation or cholesterol efflux affected the acquisition of fertilizing capacity. Phosphorylation and fertilization could be promoted by addition of MeBCD.

Beneficial effect of cholesterol supplementation

The mammalian spermatozoa are sensitive to cold shock. Irreversible damage occurs to spermatozoal membranes, during the phase transition, when spermatozoa are cooled from room temperature to 5 ^{o}C. Freezing damage is due to changes in membrane lipid composition, such as cholesterol depletion [19]. Some of this damage can be ameliorated by adding cholesterol to the membrane.

Mocé et al. have recently reviewed the effect of cholesterol supplementation on the various properties of sperm cells [20]. Adding cholesterol-loaded cyclodextrins (CLCs) to spermatozoa prior to freezing, increases cell cryosurvival. Both MeBCD and HPBCD work well as carrier of cholesterol. The cholesterol induced stabilization of the plasma membrane was demonstrated for the sperms of various animals including bull, stallion (horse), donkey, goat, ram (sheep), boar (swine) and mouse.

Both motility and viability of the CLC-treated sperms are improved after freezing and thawing. On the other hand, the CLC treatment had no beneficial effect on sperms which are not sensitive for cold shock, such as rabbit and rainbow trout, as they have higher cholesterol concentration in the membrane [21].

Concerning the functionality of sperm after freezing and thawing of the CLC-treated semen the percentage of motile sperms was enhanced even after incubation at 38.5 ^{o}C (mimicking the conditions of the female reproductive tract). In addition to the enhanced tolerance to heat also the osmotic tolerance was improved. Moreover, the membrane fluidity and permeability for cryoprotectants, such as glycerol, ethylene glycol were similar or enhanced [20].

In their review Mocé *et al.* emphasized that the beneficial effect of CLC is attributed to cholesterol and not the CD itself, as treating the sperm cells with MeBCD alone prior to freezing decreased the cryosurvival owing to the cholesterol removal from the membranes caused by the CD [20].

In spite of the improved quality of the sperms treated with CLC the fertility rate was usually not enhanced (similar or lower). The mechanism is not fully understood. The CLC treatment might change not only the cholesterol content in the lipid bilayer but the other components (phospholipids) necessary for the interaction with the female reproductive tract.

The initial step of capacitation is the loss of cholesterol. As the CLC-treated cells preserve their enhanced cholesterol content after thawing their capacitation and timing for acrosome reaction were retarded for stallion sperms but unretarded for bull sperms. It is obvious that the sperms with membrane of higher stability need more time for capacitation and acrosome reaction. That can partly explain the failure in enhancing the fertility rate with CLC-treated cells [20].

CLCs can be added to neat semen, making this technology feasible for practical application using current cryopreservation techniques [22]. CLC and 0.4 M sucrose protected the goat epididymal sperm against freezing-induced damages even without the usual cryoprotectants [23]. Recent studies aimed at optimization of the CLC treatment [24].

Conclusions

Cholesterol incorporation into sperm membranes improves the quality of cryopreserved semen by increasing the sperm membrane stability and fluidity at low temperatures. Despite the beneficial effect of cholesterol addition on sperm quality, studies demonstrate that the presence of large amounts of cholesterol in the plasma membrane interferes with the physiological process of sperm capacitation and might be detrimental to frozen sperm fertility.

On the other hand, applying MeBCD in the preincubation medium of the thawed sperms improves capacitation and fertility rate.

The combination of these two treatments (cholesterol supplementation with cholesterol-loaded MeBCD prior to freezing and cholesterol removal with MeBCD after thawing) could be beneficial for assisted reproductive technology and animal breeding industries.

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Carboxymethyl-β-cyclodextrin, Cyclic RGD Peptide, Tumor targeting ligand, Doxorubicin, PAMAM dendrimer

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Recovery of paralysis, Surgery of the thyroid gland

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Ferrocenyl group, β-Cyclodextrin, Hybrid materials, Gold nanoparticles

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Self-aggregates, Inclusion complex, TEM

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Tight junctions, CNS diseases, Drug delivery, Lipids

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Anaesthesia, Intravenous anaesthesia

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β-CD, HP-β-CD, SBE-β-CD, Inclusion complex, Solubilization, Thermal stability

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Extracellular enzyme activities, and utilization of α-cyclodextrin as carbon source, Bacterioplankton, Virus, Protozoa, Biolog

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Pulmonary surfactant, Mechanical ventilation, Surfactant protein A (SP-A), Cholesterol sequestering agent, Methyl-β-cyclodextrin, Surfactant depleted rats

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PC12 cells, Frog urinary bladder epithelial cells, Signaling, Methyl-β-cyclodextrin

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Phase-solubility method, Phenolic antioxidants

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Surface activity, Encapsulation, Water solubility, Stability

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Cosmetic use, Biochip, Adamantanyl functional groups, β-Cyclodextrins groups, Kinetic profile, Association phase, Dissociation phase, Reversible inclusion complex

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Decomposition, Alkaline earth and rare-earth element fluorides

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Concentrated emulsion polymerization, Adsorption/desorption cycles, Allyl-β-CD

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β-Cyclodextrin, Monochlorotriazinyl-β-cyclodextrin, UV-protectors, Single stage process, Eco-friendly wool prints, Nanoparticles

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Free lipase, Cyclodextrin, Candida sp. 99–125, Methanolysis, Industrialization

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β-Cyclodextrin, Covalent binding, Reusability, Wastewater

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Phenylsuccinic acid, α-Cyclohexyl-mandelic acid, Hydroxyphenyl-β-cyclodextrin, Multistage extraction, Liquid–liquid extraction, Optimization, Enantioseparation

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Fluorescence, High sensitivity for Fe^{2+}

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Aqueous solubility, Enchangement of absorbance, Inclusion complex

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Methyl-β-cyclodextrin, Acid dissociation constant, pKa shift, Chiral separation

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Methyl-β-cyclodextrin, Sulfated-β-cyclodextrin

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Multiwalled-carbon nanotubes, Carbon paste electrodes, β-CD

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Excited-state intramolecular proton transfer (ESIPT), Fluorescence probe

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Glutamic acid, Aspartic acid, β-Cyclodextrin, Binding constant

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Thymine–Hg^{2+}–thymine coordination chemistry, Cysteine, Homocysteine, Glutathione, γ-Cyclodextrin

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Chiral additive, Chiral recognition, Complexation, Enantioselectivity, Mobile phase, Monocationic cyclodextrin, Polycationic cyclodextrin, Stationary phase

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Edited and produced by: CYCLOLAB
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