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Mini Review

Clinical Applications of the Test on Acrosin Activity

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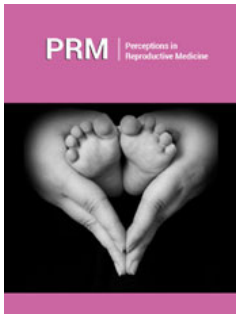

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Abstract

The acrosin activity is assayed by many reproductive medicine centers as an indicator of sperm cell functions. The result of this test is often applied for assessing the quality of spermatozoa and risk of male infertility; for the measurement of sperm cell viability in research and/or optimization of sperm cryopreservation in different species; for decision making on ICSI procedure in IVF. This minireview summarizes the detection method, the relation between acrosin activity and sperm cell morphology/function and discusses the applications of acrosin activity for research and clinical purposes. Comments on the knowledge gaps and future studies are also provided.

Keywords: Acrosin activity; Acrosome; Male infertility; ICSI

Introduction

The spermatozoa acrosome is a specialized Golgi-like organelle located at the anterior end of the spermatozoon. The acrosome contains a variety of proteinases, glycohydrolases, phosphatases, esterases and aryl sulfatases [1]. When sperms capacitated by local factors of female reproductive tract approach an oocyte, the Zona Pellucida (ZP) of the oocyte primes sperms to initiate the Acrosome Reaction (AR), an exocytotic event leading to the release of acrosome enzymes [2,3]. These enzymes will digest the components of ZP, allowing spermatozoon to penetrate the ZP and ultimately to fuse with the oocyte membrane. Acrosin is the best-studied type of Acrosome Enzymes, and its proteolytic activity is often assayed to represent the collective activities of all acrosome enzymes [4,5]. Accumulating data shows that acrosin activity can serve as an indicator of overall viability or quality of sperm samples [6-8].

Most centers of reproductive medicine apply the classical modified Kennedy method to measure acrosin activity. The method spectrophotometrically determines acrosomal l-arginine amide enzyme activity with N-α-benzoyl-DL-arginine 4-nitroanilide hydrochloride (BAPNA) as substrate [9]. In this system, acrosin hydrolyzed BAPNA to produce chromophoric 4-nitroaniline, whose absorbance was detected at 405nm on a spectrophotometer. Commercial kits are available from various biotech companies such as BERD Life Science, Shenzhen, China; Xindi Life Science, Nanjing, China. One IU of acrosin activity is defined as the amount of enzyme that hydrolyzes 1μmol BAPNA/min at 23 °C, and the acrosin activity is often expressed as μIU/10^6 spermatozoa. Cui et al. [10] investigated the methodology of acrosin assay and concluded that temperature, time of incubation, and the sperm concentration could influence the assay results [10]. Obviously, the assay detects the activity of all arginine

amidases including acrosin itself and other enzymes. Whether the changes in acrosin activity are only caused by an alteration in these proteins' quantity or the changes are related to the endogenous inhibition/activation of their catalytic activity as well could not be differentiated by currently adopted measurement procedure. Besides amidases, little is known about the changes, relationship with sperm cell functions, and potential clinical applications of other acrosome enzymes.

Acrosin protease activity is regulated by physiological or cellular factors. For example, Aguirreburualde et al. [11] observed that lysophosphatidylcholine induced acrosome exocytosis and increased the acrosin activity of spermatozoa pre-capacitated with heparin and blocking of tyrosine kinase and PKC led to reduction of acrosin activity [11]. Low levels and forced dissipation of mitochondrial membrane potential in sperm cells are associated with decreased acrosin activity [12]. Our group recently performed a high throughput proteomic analysis and identified 35 significantly upregulated and 99 downregulated proteins in human sperm cells associated low acrosin activity. Pathway analysis and verification of relating enzymes/metabolites revealed that the redox balance as well as energy production in sperm cells are important pathways affecting the acrosin activity [13]. Apparently, acrosin activity is subject to complicated regulations on the levels of expression, post-translational modification, release, and activation. Indeed, it is the intricate interactions between these regulatory mechanisms and sperm functions make it possible for acrosin activity to reflect a variety of sperm functions and morphologies.

Clinical and Research Applications of Acrosin Activity

Acrosin activity assay for assessing the quality of spermatozoa and risk of male infertility

Schill et al observed a decreased acrosin activity in patients with polyzoospermia in comparison with normozoospermic men and speculated that this alteration might indicate a functional defect of the proteolytic potential of the sperm acrosome and reduced fertility in polyzoospermia patients [14]. In 2010, measurement of acrosin activity has been added to the "WHO Laboratory Manual for the Examination and Processing of Human Semen" for evaluating the quality of spermatozoa, in addition to sperm motility/morphology assays and semen plasma biochemical assays. Nowadays most reproductive medicine centers routinely test the acrosin activity and its level is considered an important parameter of sperm function by andrologists. Nakagawa reported that acrosin activity positively correlated with sperm morphology and fertilization rate [15]. Gerhard reported that sperm density and sperm motility were significantly correlated to acrosin activity [16]. Interestingly, Chaudhury et al. [17] analyzed the free acrosin, proacrosin, and total acrosins in semen samples from unexplained infertile patients as well as from healthy fertile donors, and observed that compared to the plasma membrane and mitochondrial markers, the total acrosin activity was a more sensitive biochemical marker for clinical evaluation of unexplained infertility in males [17]. In these applications, cutoff values of 25-36μIU/10^6 sperm have been applied by reproductive medicine centers as the differentiating threshold between poor and normal sperm quality [18,19]. besides clinical application, in some epidemiological studies on infertility factors such as inflammation and obesity [20,21], decreased acrosin activity is often used as a reference for increased risk of infertility.

Acrosin activity as a biochemical parameter for optimization of sperm cryopreservation in different species

Pinart et al. Reported that acrosin activities are significantly different between good and poor freezability ejaculates, even before the freeze-thawing procedures, suggesting that acrosin activity can serve as a reliable predictor of boar sperm freezability [22]. Abigail et al. Observed that goat spermatozoa cryopreserved with slow freezing had lower abnormality, and correspondingly, higher acrosin activity, than those preserved with rapid freezing [23]. In addition, semen samples cryopreserved with Tris-based extenders containing 15% tiger nut milk also had higher acrosin activity, motility, livability and membrane integrity than those without [23]. Estrada et al. Observed that supplementing freezing media with 2mM GSH partially counteracted the cryopreservation-related decrease of acrosin activity in good freezability ejaculates but not in poor freezability ejaculates [24]. This observation suggested that the protective effects of GSH on the acrosin activity of frozen-thawed boar spermatozoa might rely on the intrinsic factors of sperms. Since most such studies focused on the comparison of effects on sperm quality by different cryopreservation reagents/procedures rather than establishing a guideline, no cutoff value of acrosin activity is available for this kind of applications.

Application of acrosin activity for IVF procedures

Jonge et al. [3] investigated the relationship between acrosin activity and semen ability of human spermatozoa to fertilize mature oocytes retrieved after hormonal stimulation. The spermatozoa ultimately fertilized ≥70% of mature oocytes had significantly greater acrosin activity ($P<0.01$) than spermatozoa ultimately fertilized < 70% of mature oocytes, suggesting that acrosin activity could be a valuable marker for assessing the sperm fertilizing potential in IVF operation [25]. Langlois et al. [19] observed that twenty percent of the morphologically normal sperms had acrosin activity lower than 25μIU/10^6 sperm, and sperm acrosin activity ($P=0.002$) effectively predicted a low in vitro fertilization rate independently of sperm morphological alterations ($P<0.001$) [19]. Xu et al. [26] observed that acrosin activity was positively correlated with normal morphology of sperm cell, and a higher acrosin activity could predict a higher in vitro fertilization rate when patients were divided into 3 groups of ≥25μIU/10^6 spermatozoa, 14-25μIU/10^6 spermatozoa and <14μIU/10^6 spermatozoa. The authors recommended that early rescue ICSI, half ICSI, or full ICSI should be considered in advance for patients with spontaneous acrosome reaction rates ≥9.52% or with spontaneous acrosome reaction rates ≥9.52% plus acrosin activities <25μIU/10^6 spermatozoa. A recent study by Hu et al indicated that sperm acrosin activity could serve as an effective prognostic indicator for choosing between IVF and Intracytoplasmic Sperm Injection (ICSI) in clinical practice [27].

For patients with acrosin activity below 24.78μIU per 10^6 sperm, ICSI procedure significantly increased the fertilization rate, normal fertilization rate, and good-quality embryo rate in comparison with the conventional IVF procedure. The authors concluded that one promising application of acrosin activity could be for the selection of ICSI over conventional IVF for infertile male patients with low fertilization rate or complete fertilization failure [27].

Concluding Remakes

Among the numerous semen tests routinely performed in andrology laboratory, the acrosin activity test is recognized as one of the most useful assay for clinical as well as research purposes. By its close association with sperm cell functions, acrosin activity is increasingly applied for assistant diagnosis, prognosis and decision making in IVF practice. For different applications, divergent cutoff values as well as their sensitivities and specificities should be determined. A combination of acrosin activity with clinical parameters or results of other laboratory tests may improve the efficiency of acrosin activity as an indicator of sperm quality. Also, if future studies could develop specific test method for individual acrosome enzymes and clarify their different roles for fertilization, more and better clinical applications can be anticipated. A specific test for certain acrosome enzyme may help us to stratify male infertility into better-defined subtypes, and may even provide a basis for targeted therapy.

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