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Review Article

Steroid receptors and their ligands: Effects on male gamete functions

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ABSTRACT

In recent years a new picture of human sperm biology is emerging. It is now widely recognized that sperm contain nuclear encoded mRNA, mitochondrial encoded RNA and different transcription factors including steroid receptors, while in the past sperm were considered incapable of transcription and translation. One of the main targets of steroid hormones and their receptors is reproductive function. Expression studies on Progesterone Receptor, estrogen receptor, androgen receptor and their specific ligands, demonstrate the presence of these systems in mature spermatozoa as surface but also as nuclear conventional receptors, suggesting that both systemic and local steroid hormones, through sperm receptors, may influence male reproduction. However, the relationship between the signaling events modulated by steroid hormones and sperm fertilization potential as well as the possible involvement of the specific receptors are still controversial issues.

The main line of this review highlights the current research in human sperm biology examining new molecular systems of response to the hormones as well as specific regulatory pathways controlling sperm cell fate and biological functions. Most significant studies regarding the identification of steroid receptors are reported and the mechanistic insights relative to signaling pathways, together with the change in sperm metabolism energy influenced by steroid hormones are discussed.The reviewed evidences suggest important effects of Progesterone, Estrogen and Testosterone and their receptors on spermatozoa and implicate the involvement of both systemic and local steroid action in the regulation of male fertility potential.

Contents

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Introduction

The study of steroid effects on the activation of sperm is object of intense investigative efforts attempting to identify the "putative" receptors and the molecular mechanisms involved in the process of fertilization.

Spermatozoa were considered genomically inert cells, in which all the major classes of steroids showed non-classic rapid actions [87]. However, in recent years a new picture of these cells is emerging, due to the demonstration of the expression of nuclear steroid receptors and their ligands [120,10–12,54] together with their effects on sperm physiology. Despite this, different avenues remain to be extended to the biology of this cell type.

Induction of the acrosome reaction [99,76], rapid increases in sperm motility [115], and resumption of oocyte maturation in fish and amphibian species [70,117] are examples of nonclassical steroid actions. The first demonstration of such effects on spermatozoa occurs when Calzada et al. [26] demonstrated an increase of the membrane potential upon treatment with Testosterone (T), Estrogens (E) and Progesterone (Pg). One year later, Osman et al. [90] reported the rapid induction of acrosome reaction by Pg and 17OH-Pg in human spermatozoa. Similar effects were observed using non-permeable Pg conjugates and classical Progesterone Receptor (PR) antagonists such as mifepristone (also known as RU487) counteracted these special actions.

Actually an extensive and comprehensive information regarding the regulation of sperm fertilization potential by steroid hormones and their receptors is available, although controversial data are often reported in this issue [36,37,33,122].

Spermatogenesis is retained the most important target of steroid hormones, nonetheless recent studies demonstrate their ability to influence the fertility through the modulation of sperm capacitation process [134]. Despite the data indicating that responsiveness to steroid hormones is related to fertilization, the role of steroids as physiological activators of sperm is still discussed by scientists. Several experimental studies evidence the molecular pathways activated by steroid hormones in spermatozoa (reviewed by Revelli et al. [94]); however the identity of sperm specific receptors is under investigation.

Sperm survive in a resting state in male genital region and the seminal plasma itself contributes to maintain this quiescent condition. During the transit in the female genital tract, human sperm acquire the competence to fertilize the oocyte through the capacitation process, a series of bio-molecular changes able to influence human sperm physiology. The switch from uncapacitated into capacitated status implies an increased metabolism and overall energy expenditure probably responsible of specific changes in sperm function. Several studies clarify the relationship between the signaling events associated with capacitation and the change in sperm metabolism energy, influenced by steroid hormones and the possible involvement of specific receptors ([18,121,37]).

These topics acquire more emphasis since recently the decline of male fertility, due to the potential effect of estrogens and endocrine disruptors, indicates steroid receptors as targets of new pharmacological tools with beneficial effects but also with potential toxicity when administered at high doses, as nearly pure compounds [38].

The present review analyzes the main discoveries regarding the steroid hormones and specific receptors in human sperm biology, the molecular pathways involved, the patho-physiological relevance of the effects of these hormones and the possible involvement of receptors on male gamete metabolism and fertilization potential.

Progesterone Receptor

Identification and localization in human sperm

In the female reproductive tract, mammalian sperm are most likely exposed to Pg [93]. The follicular fluid, mixed with the oviduct fluid or the extracellular matrix of the *cumulus oophorus*, trap Pg which acts on spermatozoa at the fertilization site [91,98]. In mice Pg enhances the acrosomal exocytotic response of sperm to the subsequent exposition to the zona pellucid glycoprotein ZP3 [96]. Also Pg has been observed to increase the percentage of spermatozoa exhibiting hyperactivated motility at very low concentrations (3.1 ng/ml) and within 10 min of addition to the incubation medium [124], and to increase the velocity of spermatozoa when added to peritoneal fluid [84]. Several studies (reviewed by Baldi et al. [16]) support the rapid, nongenomic actions of Pg, initiated at the surface of human and other mammalian sperm, although the current knowledge in the field requires further investigations to better define the Pg effects on sperm functions.

Initially Pg sperm-binding sites were evidenced on the plasma membrane of the spermatozoon [20]. Later studies using antibodies directed against the C-terminal region of the conventional PR, revealed, by Western blot analysis, proteins of 51–57 kDa in sperm lysate [19,21,108,80], and a 52-kDa antigen has been found on the spermatozoa head [114]. A 55-kDa protein in testicular and