Modeling of progesterone-induced intracellular calcium signaling in human spermatozoa

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HIGHLIGHTS

- We propose a mathematical model to quantify Ca^{2+} dynamics in human spermatozoa by progesterone.
- Dynamic modeling for progesterone-activated CatSper Ca^{2+} channels is proposed.
- Two calcium stores including RNE and CRV are included in the mathematical modeling.

ARTICLE INFO

ABSTRACT

Calcium ion is a secondary messenger of mammalian spermatozoa. The dynamic change of its concentration plays a vital role in the process of sperm motility, capacitation, acrosome and fertilization. Progesterone released by the cumulus cells, as a potent stimulator of fertilization, can activate the calcium channels on the plasma membrane, which in turn triggers the dynamic change of intracellular calcium concentration. In this paper, a mathematical model of calcium dynamic response in mammalian spermatozoa induced by progesterone is proposed and numerical simulation of the dynamic model is conducted. The results show that the dynamic response of calcium concentration predicted by the model is in accordance with experimental evidence. The proposed dynamic model can be used to explain the phenomena observed in the experiments and predict new phenomena to be revealed by experimental investigations, which will provide the basis to quantitatively investigate the fluid mechanics and biochemistry for the sperm motility induced by progesterone.

1. Introduction

The sperm motility, capacitation (Yanagimachi, 1994), hyper-activation (Ho and Suarez, 2001) and acrosome reaction (Wassarman et al., 2001; Yanagimachi, 1994) are the essential processes for spermatozoa to penetrate and fertilize an oocyte. During these processes, the intracellular calcium signaling induced by progesterone has been shown to play a vital role (Harper et al., 2003; Ho and Suarez, 2001; Oren-Benaroya et al., 2008; Teves et al., 2009).

Progesterone, a critical hormone released by cumulus cells surround egg, can stimulate the intracellular calcium signaling in spermatozoa that regulates chemotaxis, capacitation, flagellar-beat mode (including hyperactivation) and acrosome reaction (Publicover et al., 2007), which in turn activates the inactive

spermatozoa and makes them swim to egg continuously and finally have the ability to penetrate and fertilize egg. The exact mechanisms for progesterone-induced calcium signaling are not fully understood. It has already been shown that progesterone activates Ca^{2+} influx from the CatSper channels (Publicover and Barratt, 2011; Strünker et al., 2011) and induces additional Ca^{2+} release from the calcium stores including redundant nuclear envelope (RNE) and calreticulin-containing vesicles (CRV) in the neck region through IP_3-gated Ca^{2+} channels and the Ca^{2+}-induced Ca^{2+} release (CICR) mechanism (Costello et al., 2009; Publicover et al., 2007). Recently, Strünker and his colleagues (Strünker et al., 2011) used the technique of whole-cell patch clamping to observe the influence of progesterone of different concentrations on intracellular calcium response. Their experimental results provided compelling evidence that progesterone directly acted on the calcium channels on the plasma membrane and sequentially induced immediate influx of Ca^{2+} into sperm, or indirectly activated Ca^{2+} release from intracellular stores to the cytoplasm or both, and even at low concentration progesterone

can induce immediate influx of Ca^{2+}. Lishko and her colleagues (Lishko et al., 2011) adopted patch clamping to investigate the dose dependence of potentiation of inward current $I_{CatSper}$ through the CatSper channels by progesterone, which made a significant contribution to understand the quantitative relationship between CatSper open and dose of progesterone. In several other experiments, it had been observed that exposure of human spermatozoa to stepped or gradient progesterone induced Ca^{2+} oscillations (Alasmari et al., 2013; Bedu-Addo et al., 2008; Harper et al., 2004), which are essential for sperm motility and reorientation because they may prompt spermatozoa to undergo a sharp turning event in vivo (Espinal et al., 2011).

Mathematical modeling of intracellular calcium signaling in human spermatozoa allows us not only to explain existing phenomena about calcium response but also to explore scenarios that may be difficult to be investigated in experimental studies. Upto now, very few mathematical models of intracellular calcium signaling in spermatozoa have ever been proposed in the literature. A groundbreaking mathematical model of CatSper channel mediated calcium dynamic response in mouse spermatozoa was proposed by Olson and her colleagues (Olson et al., 2010, 2011). In this pioneering work, the effect of cyclic adenosine monophosphate (cAMP) on the activation of CatSper channels and the release of Ca^{2+} from the RNE was documented, and the experimental results by Xia and his co-workers (Xia et al., 2007) were well reproduced. In the experiment, cAMP analog was considered as a stimulus to mouse sperm and induced Ca^{2+} influx into the principal piece, resulting in an increase in the intracellular Ca^{2+} concentration, $[Ca^{2+}]_{in}$. The rapid Ca^{2+} increase starts in the principal piece and followed by a higher sustained Ca^{2+} concentration in the midpiece and the head by Ca^{2+} diffusion and CICR mechanisms.

However, in all the previous mathematical models, progesterone-induced CatSper channel dynamics was missing because progesterone has never been considered as a stimulus. Furthermore, only the calcium store RNE was included while another essential calcium store CRV was ignored, which would be of importance to reproduce some other critical experimental phenomena, e.g., exposure of human spermatozoa to a 3 μM progesterone may induce slow Ca^{2+} oscillations, observed in many experimental studies (Bedu-Addo et al., 2008; Harper et al., 2004; Lishko et al., 2011; Strünker et al., 2011).

In this paper, we are to build a novel mathematical model for intracellular calcium dynamic response in human spermatozoa. Both a constant and gradient concentration of progesterone will be used as the stimulants to open CatSper channels (Harper et al., 2004), and the dynamics for progesterone-induced Ca^{2+} influx and Ca^{2+} release from the CRV (Publicover et al., 2007) will be included in our dynamic model. Hopefully, the aforementioned critical experimental phenomena especially the Ca^{2+} oscillation (Bedu-Addo et al., 2008; Harper et al., 2004) can be reproduced by the dynamic model. The proposed dynamic model will provide the basis for not only quantitatively investigating the fluid mechanics and biochemistry for the sperm

motility induced by progesterone but also better describing the dynamical process of fertilization in vivo.

2. Model development

2.1. Formulation of governing equations

In human spermatozoa as shown in Fig. 1, intracellular calcium homeostasis is maintained by the amount of Ca^{2+} influx through Ca^{2+} channels on the cell membrane from extracellular space into the cytosol, the amount of Ca^{2+} outflow from intracellular calcium stores into the cytosol, the amount of Ca^{2+} inflow into calcium stores, and the amount of Ca^{2+} outflow from cytosol to the extracellular space by Ca^{2+} clearance mechanisms (Olson et al., 2011). Ca^{2+} channels include CatSper Ca^{2+} channels, voltage-operated Ca^{2+} channels (VOCC), transient receptor potential channels (TRPC), cyclic nucleotide-gated channels (CNG) and so on (Wiesner et al., 1998; Castellano et al., 2003). Ca^{2+} clearance mechanisms include the plasma membrane Ca^{2+} ATPase (PMCA), the Na^+/Ca^{2+} exchanger (NCX), the mitochondrial Ca^{2+} uniporter (MCU) and so on (Wennemuth et al., 2003). The Ca^{2+} stores locate in the neck region, including RNE and CRV, both of which have IP_3-gated Ca^{2+} channels and CICR mechanism (Costello et al., 2009; Publicover et al., 2007) and may release calcium ions into cytosol. Meanwhile, a secretory pathway Ca^{2+}-ATPase (SPCA) is likely to cause the clearance of Ca^{2+} in the cytosol back into the Ca^{2+} stores (Olson et al., 2010).

When human spermatozoa are exposed to progesterone stimulation, the CatSper channels are directly activated and the calcium stores can be indirectly motivated by progesterone (Koulen et al., 2008; Publicover et al., 2007; Strünker et al., 2011). The Ca^{2+} diffusion due to its concentration difference will induce the intracellular Ca^{2+} dynamic response in spermatozoa.

2.1.1. Model for intracellular calcium dynamics

To model the intracellular calcium dynamics, it is assumed that: (i) the hydrodynamic factors are neglected as the sperm is stationary (Olson et al., 2011), (ii) the sperm is slender and only allows a 1-dimensional longitudinal reaction-diffusion (Olson et al., 2011), and (iii) only the fluxes of CatSper and PMCA channels are considered compared to other Ca^{2+} channels and Ca^{2+} clearance mechanisms (Wennemuth et al., 2003; Olson et al., 2011).

Based upon the above assumptions, the equation governing 1-dimensional Ca^{2+} reaction-diffusion can be expressed as (Olson et al., 2010)

$$\frac{\partial C}{\partial t} = D_{Ca}\frac{\partial^2 C}{\partial x^2} + J, \tag{1}$$

where C is the intracellular Ca^{2+} concentration, t is time, x is the length along the sperm starting with the head, D_{Ca} is the effective
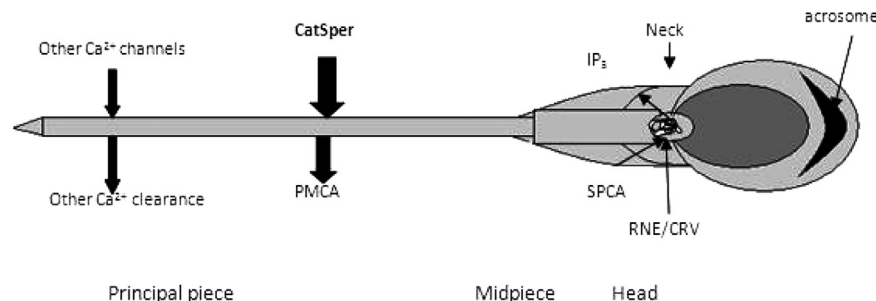

Fig. 1. A schematic of Ca^{2+} channels and Ca^{2+} clearance mechanism. The directions of arrows indicate the most common directions of Ca^{2+} flow, the size of an arrow is in direct proportion to its effect. The chief channels and pumps we consider about are CatSper channels and PMCA.