A Model of CatSper Channel Mediated Calcium Dynamics in Mammalian Spermatozoa

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Abstract CatSpers are calcium (\(\text{Ca}^{2+}\)) channels that are located along the principal piece of mammalian sperm flagella and are directly linked to sperm motility and hyperactivation. It has been observed that \(\text{Ca}^{2+}\) entry through CatSper channels triggers a tail to head \(\text{Ca}^{2+}\) propagation in mouse sperm, as well as a sustained increase of \(\text{Ca}^{2+}\) in the head. Here, we develop a mathematical model to investigate this propagation and sustained increase in the head. A 1-d reaction-diffusion model tracking intracellular \(\text{Ca}^{2+}\) with flux terms for the CatSper channels, a leak flux, and plasma membrane \(\text{Ca}^{2+}\) clearance mechanism is studied. Results of this simple model exhibit tail to head \(\text{Ca}^{2+}\) propagation, but no sustained increase in the head. Therefore, in this model, a simple plasma membrane pump-leak system with diffusion in the cytosol cannot account for these experimentally observed results. It has been proposed that \(\text{Ca}^{2+}\) influx from the CatSper channels induce additional \(\text{Ca}^{2+}\) release from an internal store. We test this hypothesis by examining the possible role of \(\text{Ca}^{2+}\) release from the redundant nuclear envelope (RNE), an inositol 1,4,5-trisphosphate (IP\(_3\)) gated \(\text{Ca}^{2+}\) store in the neck. The simple model is extended to include an equation for IP\(_3\) synthesis, degradation, and diffusion, as well as flux terms for \(\text{Ca}^{2+}\) in the RNE. When IP\(_3\) and the RNE are accounted for, the results of the model exhibit a tail to head \(\text{Ca}^{2+}\) propagation as well as a sustained increase of \(\text{Ca}^{2+}\) in the head.

Keywords Calcium · Reaction-diffusion · CatSper channels · Spermatozoa motility · Inositol 1,4,5-trisphosphate

Abbreviations

IP\(_3\) inositol 1,4,5-trisphosphate
RNE redundant nuclear envelope
IP\(_3\)R inositol 1,4,5-trisphosphate receptor
\(\text{Ca}^{2+}\) Calcium

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1. Introduction

Intracellular calcium (Ca\(^{2+}\)) signaling has been studied and modeled for many years in somatic cells (Berridge, 2005). In spermatozoa, the exact mechanisms of Ca\(^{2+}\) signaling are unknown and are currently being investigated (Jimenez-Gonzalez et al., 2006). Experimentally, it has been shown that the intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]) in sperm regulates motility and hyperactivation (Carlson et al., 2005; Ho and Suarez, 2001b; Suarez, 2008), capacitation (Visconti, 2009), and the acrosome reaction (Kirkman-Brown et al., 2003). Spermatozoa must undergo the acrosome reaction, the fusion of the acrosomal membrane with the outer plasma membrane (see Fig. 2), which requires increased intracellular [Ca\(^{2+}\)] in the head, to penetrate and fertilize the egg (Kirkman-Brown et al., 2003). Increases in intracellular [Ca\(^{2+}\)] can trigger sperm hyperactivation, motility characterized by an increased flagellar bend amplitude and beat asymmetry, enabling the sperm to reach the oocyte and to penetrate the oocyte zona pellucida (Quill et al., 2003; Ren et al., 2001; Stauss et al., 1995; Ho and Suarez, 2001b). Capacitation is a series of fast and slow processes that imparts on the sperm the ability to fertilize the egg (Visconti, 2009). Initiation and regulation of sperm motility have been observed as a result of changes in intracellular cyclic adenosine monophosphate (cAMP), Ca\(^{2+}\), and pH (Aoki et al., 1999; Ishijima et al., 2006; Marquez and Suarez, 2004; Marquez et al., 2007). Note that these changes may be dependent on extracellular Ca\(^{2+}\) concentration.

Signals are produced by the opening of Ca\(^{2+}\) channels in the plasma membrane, in the membrane of Ca\(^{2+}\) storage organelles, or both, acting together (Berridge, 2005; Felix, 2005; Jimenez-Gonzalez et al., 2006). Channel activity can be modulated by other ions and enzymes, influencing the rates and direction of ion flow through channels and exchangers, which in turn affect intracellular pH, Ca\(^{2+}\), and other second messengers (Darszon et al., 2001). Ion channels are key signaling elements in spermatozoa since motility, maturation, and the acrosome reaction can also be inhibited by certain channel blockers (Publicover and Barratt, 1999). Spermatozoa possess intricate mechanisms for regulation and coordination of Ca\(^{2+}\) signals (Jimenez-Gonzalez et al., 2006).

The exact mechanisms and pathways by which Ca\(^{2+}\) controls motility in a sperm flagellum are not completely known, but the importance of intracellular [Ca\(^{2+}\)] on motility and hyperactivation has been established (Felix, 2005; Ishijima et al., 2006; Smith, 2002; Suarez, 2008). Using a Ca\(^{2+}\) sensitive fluorescent dye, intracellular [Ca\(^{2+}\)] was observed to be higher in the head and in the flagellar midpiece of hyperactivated sperm, as compared to nonhyperactivated sperm (Suarez et al., 1993). Suarez et al. (1993, 2008) hypothesized that increases in intracellular [Ca\(^{2+}\)] initiates and maintains hyperactivation.

The CatSper family of proteins form heterotetrameric, pH, and voltage dependent Ca\(^{2+}\) permeable ion channels that are sperm specific and required for male fertility (Carlson et al., 2005; Quill et al., 2003; Qi et al., 2007; Ren et al., 2001; Xia et al., 2007). The CatSpers are located on the plasma membrane of the principal piece, the largest segment of the flagellum (Fig. 2) (Quill et al., 2003; Ren et al., 2001; Xia et al., 2007). Four different proteins have been identified: CatSper-1 (Ren et al.,...