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Potential role of Catsper and proton ion channels in bull fertility

Jayashree Gogoi, Mohan Mondal, Prasanna Pal, VR Upadhyay, Piyali Kuri, Indranil Mukherjee and Sachin Tripura

Abstract
Sperm ion channels play a key role in animal fertility. For successful fertilization, sperm motility, chemotaxis, capacitation and the acrosome reaction are few of the important attributes contribute significantly towards bull fertility. Elevation of sperm intracellular pHandCa^{2+}are vital for these key events in the fertilization process. Sperm ion channels such as catsper, help in regulating the Ca^{2+} entry, and proton channels such as hv1 is the main proton extrusion pathway that maintain the sperm intracellular ph. Ion channels are deeply involved in the interaction between sperm, environmental cues and the egg. Study of ion channels in sperm promises to open a new horizon for identification of factors determining sperm fertility and causes of infertility. Understanding of the molecular mechanisms of the ion channels regulating sperm motility would pave the way to identify novel targets for treating bovine infertility.

Keywords: Bull fertility, Catsper, proton channel, sperm ion channels

Introduction
Ion channels are pore-forming proteins that help regulate membrane potential by allowing the flow of ions across membranes, either plasma membranes or the membranes of intracellular organelles (Bertili and Bertili, 2001) [4]. Thus, by regulating intracellular ionic concentration these ion channels play a central role in various cellular processes such as maintaining the intracellular pH, osmotic balance, shaping action potential and many other cellular functions in the cell organelles (Shukla *et al*., 2012) [57]. Many ion channels are classified based on what closes or opens them. Most Na, K, Ca and some Cl channels are gated by voltage but others such as certain K, Cl channels, TRP channels, ryanodine receptors and IP3 receptors are gated by second messengers like GABA, 5 – hydroxyl tryptamine (5-HT) and they are classified as the ligand gated channels (Collingridge *et al.*,2009) [10]. These ion channels are found in various germ cells including the sperm cells and thus play a crucial role in reproduction thereby male fertility (Shukla *et al*., 2012) [57]. The key to species survival is reproduction. It begins with the fertilization of two haploid gamets (ovum and spermatozoa) produced from the ovary and testes leading to the development of a new diploid organism (Lishko and Mannowetz, 2018). Sperms are dynamic cells that are produced in the seminiferous tubules of the testes through a process known as the spermatogenesis. Spermatogonia, the most immature of the germ cell undergo continuous mitotic and meiotic changes and thus differentiate into mature spermatozoa. After formation of spermatozoa, they are deposited into the epididymis where they undergo complex maturational changes such as absorption of the fluid, increased capacity for glycolysis, changes in intracellular pH and calcium content, modification of adenylate cyclase activity, alterations in cellular phospholipid and phospholipid like fatty acid content to attain the ability to swim and fertilize the egg (Gervasi and Visconti, 2017) [19]. In bovines, the transit of spermatozoa through the epididymis takes 9-14 days (Hafez and Hafez, 2013) [20]. The morphologically mature, densely packed mammalian spermatozoa before ejaculation are stored in a quiescent state in the caudal portion of the epididymis and vas deferens (Gervasi and Visconti, 2017) [19]. The seminiferous tubules and rete testis, have a pH of 7.2-7.4, which become 6.5 in caput epididymis and 6.7-6.8 in cauda epididymis (Shum *et al*., 2011; Ng *et al*., 2018) [58]. The maintenance of the alkaline pH in the epididymis and the quiescence factor helps the spermatozoa that are transcriptionally silent to maintain their molecular and functional integrity for longer duration (Kirichok and Lishko, 2011) [27, 28]. Spermatozoa mixed with seminal plasma after maturation is ejaculated from the caudal epididymis.

Their normal motility is initiated for the first time. Sperm motility at this time is characterized by relatively low-amplitude, symmetrical tail bending when compared with hyperactivation, which is characterized by the high-amplitude, asymmetrical tail bending, observed close to the site of fertilization (Suarez, 2008) [61]. For the sperms to acquire the ability of fertilization, they require a period of incubation in the female reproductive tract. During this period, sperm undergo a series of biochemical transformations, collectively known as capacitation. It involves changes such as increase in the plasma membrane fluidity, increase in intracellular ions and protein tyrosine phosphorylation through recruitment of tyrosine kinases, generation of reactive oxygen species and the elevation of basal levels of sperm pH and (Ca2+) (Esteves and Miyaoska, 2015) [15]. The capacitated spermatozoa acquire hyperactive motility. For the sperm to find and reach the egg successfully, the egg releases certain chemo attractants such as progesterone, prostaglandins from the follicular fluid of the oocyte to reach its destination by a process known as chemotaxis. Even though they are endowed with wonderful machinery, for most sperm this adventurous journey will end nowhere. Just a few sperms will locate the egg from the millions of sperm released by a male to trigger the critical event of fertilization. The sperm must also avoid fusing with the any other cells other than the egg. The sperm behavior and metabolism are influenced by concentration of ions, pH, temperature, and other physicochemical variables. After reaching the site of fertilization the fusion of the egg and the spermatozoa are facilitated by the acrosome reaction (AR), a Ca^{2+}dependent exocytotic event that involves the fusion of the plasma and outer acrosomal membranes of the sperm head. The fusion of the sperm head with the zona pellucida results in exposure of the sperm's inner acrosomal membrane and causes the release of acrosomal enzymes needed for penetration of the egg plasma membrane. When sperm are deposited into the female reproductive tract, activation of motility is triggered by ionic or osmotic changes and on rapid intraflagellar ion changes. These transduction events are likely to involve sperm ion channels (Morisawa, 1994). Sperm intracellular pH, membrane voltage and calcium concentrations (Ca2+) are regulated by ion channels and transporters and thus are vital for sperm survival and fertility (Yanagimachi and Usui, 1974; Babcock *et al*., 1983) [71, 3]. The whole-cell patch-clamp technique, bioinformatics approaches, genetic model's molecular approaches has brought about a quantum leap in our understanding of the sperm ion channels among which include calcium, potassium, proton, nonselective and various ligand-gated channels have been identified and characterized (Lishko *et al*., 2016) [35]. Regarding the role of ion channels in sperm physiology, extensive studies have been done in human and murine species. These studies have paved the path for understanding the role of sperm ion channels in animal fertility including bovines, goats, equines and swine too. Although research is scarce, we have reviewed the literature on ion channels with special reference to catsper and proton channels and their role in regulating bull fertility.

Morphology of the sperm cells in animals

Sperm cells since their early discovery back in the 1677 by Leeuwenhoek have fascinated the researchers because of their diversity in their morphology and also in terms of their mechanism that drive their physiology (Miller *et al*.,2015) [42]. Sperm cells consist primarily of the head and the tail (flagellum) (Fig. 1). The sperm head comprises a condensed nucleus, a redundant nuclear envelope and an acrosomal vesicle. The shape and size of the sperm head varies among species from the spatula-like head in primates and ruminants to the hook-like pointed head in rodent sperm (Lishko *et al*., 2016) [35]. The flagellum has a specialized cytoskeleton called an axoneme surrounded by specialized structural components and is subdivided into three functional parts: a mitochondria-containing midpiece, a principal piece, and the endpiece. Axoneme filament runs throughout the tail. The core of the axenome consists of two central microtubules surrounded by a row of nine doublet microtubules. One microtubule of each doublet is complete, having 13 protofilaments; the other is C-shaped and has only 11 protofilaments which are made exclusively of the dimeric protein tubulin. Dynein arm motor complexes allow microtubule to slide against each other. This causes the synchronized shortening and extension of the microtubule on opposite site of the axoneme allowing the flagellum to bend. Alteration of this bending action creates the beating motion of swimming sperm.

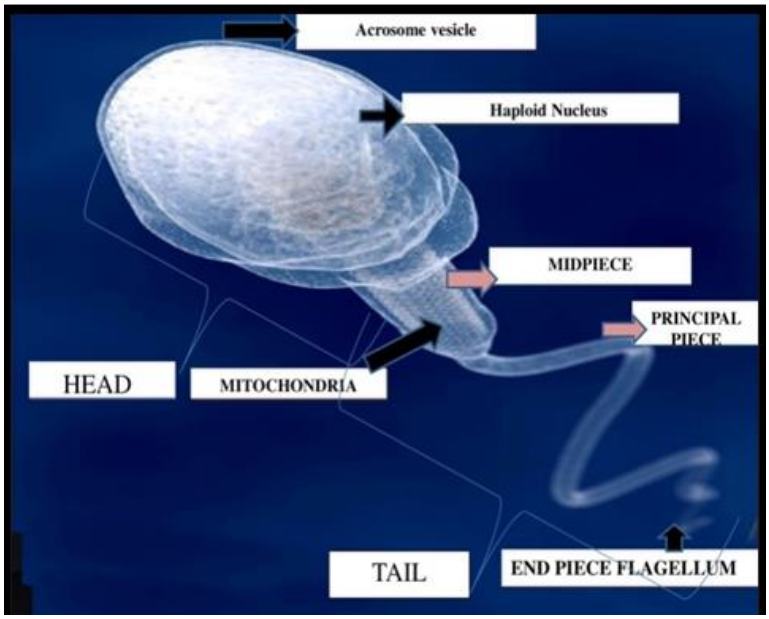

Fig 1: Morphology of the sperm cells

Fig 1: The sperm head consist of haploid nucleus and the acrosome vesicle. the region next to the head is the midpiece. The region between the midpiece and the flagellum is the principal piece. The midpiece consists of the mitochondria. Pic courtesy: Google image

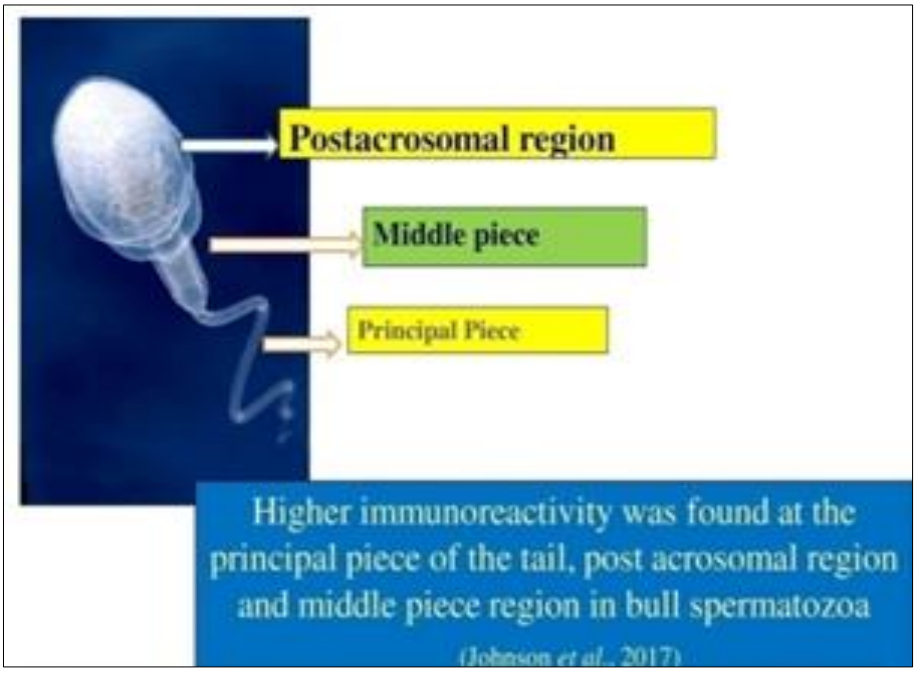

Fig 2: Localization of the catsper channels

Figure 2: CATSPER 1–4 is expressed in the testes of the bull. Localized to the principal piece of sperm tail of human, mice, boar spermatozoa. CATSPER 1–4 messenger RNA (mRNA) was expressed in the reproductive tract of the bull with highest expression in the parenchyma testis

Mode of action of Catsper

Sperm specific K^+ channel (SLO_3) maintains flagellar membrane potential. Sperm Na^+/H^+ exchangers (NHEs) through cyclic adenosine monophosphate (cAMP) play a role on sperm fertility, while cAMP is generated in the process that bicarbonate (HCO_3) activates atypical soluble adenylate cyclase (sAC) (Singh *et al.*,2015) [59]. The Catsper channel is triggered by increasing intracellular pH which depends on sNHE and Voltage-gated H+ channel 1 (Hv1) channel pumping H^+ out of sperm. Calcium balance in the sperm is maintained by Na^+/Ca^{2+} exchanger and Ca^{2+}ATPase exchanger (Singh *et al.*, 2015) [59]. The Na^+/Ca^{2+} exchanger exports one Ca^{2+} ion out of sperm and allows the entry of three Na^+ ion, however, Ca^{2+}ATPase is a Ca^{2+}/H^+ exchanger that removes intracellular Ca^{2+} and permits H^+ entry into the sperm cell. Both sNHE and Hv1 channels are positive regulator of the Catsper channel, while Ca^{2+}ATPase is a negative regulator of the Catsper channel (Sun *et al*., 2017) [62]. Activation of spermatozoa requires reduction of H+ and elevation of Ca2+ and vice versa suppresses the activity of the sperm cell. The balance between them is maintained by H+ and Ca2+ pumps or mainly determined by Ca^{2+} and hydrogen ion channels (Darszon *et al*., 2006) [13]. Marquez and Suarez (2007) [41] confirmed that extracellular application of cell permeant NH_4Cl caused the elevation of intracellular pH, which results Ca^{2+} influx and induces sperm hyperactivation in bovine, but NH4Cl has no effect on human sperm hyperactivation (Alasmari *et al*., 2013) [1]. Spermatozoa have primarily two flagellar Ca^{2+} transport proteins that balance the concentration of Ca^{2+} in the sperm flagellum. Ca^{2+} ATPase helps pumps Ca^{2+} out of the spermatozoon and CatSper channel allows the entry of extracellular Ca^{2+} inside the spermatozoon (Okunade *et al*., 2004; Schuh *et al*., 2004) [47, 56]. Ca^{2+}ATPase pumps hydrolyze ATP to export a cytoplasmic Ca^{2+}ions and to import extracellular protons. This causes acidification of flagellar cytoplasm which must be prevented by proton extrusion via proton channels (Lishko *et al*., 2012) [33, 34]. The regulation of CatSper channel involves the close association of other ion channels, such as Hv1, K+ channel of spermatozoa (Ksper/SLO3 in mouse) and ion pumps, such as $Na+/Ca^{2+}$ exchanger (Lishko *et al*., 2012) [33, 34] (fig 3).The intracellular Ca^{2+} and sperm Na+/H+ exchanger complex, the activity of which is found to be highly pronounced in epididymal sperm compared with ejaculated sperm (Rufo *et al*., 1984) [53] works in close association with Catsper complex. Ca^{2+} passing through the capacitated sperm plasma membrane inactivates a Na+/K+-ATPase bonding to the membrane. This inactivated ATPase can no longer pump Na+ away, resulting in a rapid intracellular Na+ accumulation that would in effect induce H+ efflux via a plasma membrane-associated Na +/H+ anti-porter (Fraser, 2010) [17]. An increase in concentration of intracellular Na+ could reverse a plasma membrane associated $Na+/Ca^{2+}$ anti-porter, allowing more Ca^{2+} to enter the sperm (Hyne *et al*., 1984) [23]. Thus $Na+/Ca^{2+}$ exchanger is efficient in maintaining Ca^{2+} homeostasis by its bimodal operation of ion imports and export (Krasznai *et al*., 2006; Wennemuth *et al*., 2003) [30, 70]. The role of HCO_3^- influx system for sperm capacitation is essential to maintain the pH by the inward movement of HCO_3^-. The inward movement of HCO_3^- produces cAMP by activating soluble adenylate cyclase (sAC) which promotes alkalinization and membrane hyperpolarization. Also, $HCO3^-$ entrance in sperm cytoplasm requires the presence of Cl^- and Na^+. Hence sperm capacitation depends on Cl^-, Na^+ and HCO_3- concentration. The role of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate(cGMP) in induction of Ca^{2+}

influx through CatSper is controversial as there is no clear evidence suggesting a role of cyclic nucleotide in elevation of Ca^{2+}. Somanath and Gandhi *et al*., 2000 indicated the involvement of GABA/Cl- channel for the entry of Ca^{2+} during progesterone induced in goat sperm. Calcium stores of acrosome vesicle and the redundant nuclear envelope, however, may also contribute to sperm intracellular Ca^{2+}signaling (Costello *et al*., 2009; Ho and Suarez, 2001; Suarez, 2008) [11, 21, 61]. The presence of a functional CatSper channel does not guarantee that it is regulated similarly in different species. Bovine and equine sperm are both sensitive to intracellular alkalization, resulting in an influx of Ca^{2+} into the cell. Progesterone promoted a rise in intracellular Ca^{2+} in goat sperm and addition of nifedipine just prior to progesterone induction, significantly inhibited both intracellular Ca^{2+} rise and exocytosis suggesting that Ca^{2+} channels are involved in the process (Somnath and Gandhi *et al*., 2002) [60]. Progesterone and prostaglandins in humans stimulate Ca^{2+}influx through direct action of CatSper (Brenker *et al*., 2012; Lishko *et al*., 2011) [6, 32]. Progesterone is released by the ovaries, and the cumulus cells surrounding the egg. It initiates a high Ca^{2+} influx into human spermatozoon that eventually results in the initiation of sperm hyperactivation and subsequently the acrosome reaction to reach the prerequisite for successful fertilization. CatSper channel of murine spermatozoa is not sensitive to the activators of human CatSper, such as progesterone and prostaglandins (Lishko *et al*., 2011, Blackmore *et al*.,1990) [32, 5]. Experiments using gel-purified zona pellucidas indicate that ZP3 exclusively acts as a Ca^{2+} influx-inducing protein in bovine and mouse sperm (Arnoult *et al*., 1996) [2]. However, study conducted by Loux *et al*., 2014 [38] revealed that that these compounds are not associated with Ca^{2+} influx or onset of hyperactivated motility in horse sperm. Boar spermatozoa donot massively capacitate upon exposure to bicarbonate (Saravia *et al*., 2007) [54] or to the progesterone-containing oviductal fluid (Tienthai *et al*., 2004) [64] despite displaying progesterone membrane receptors.

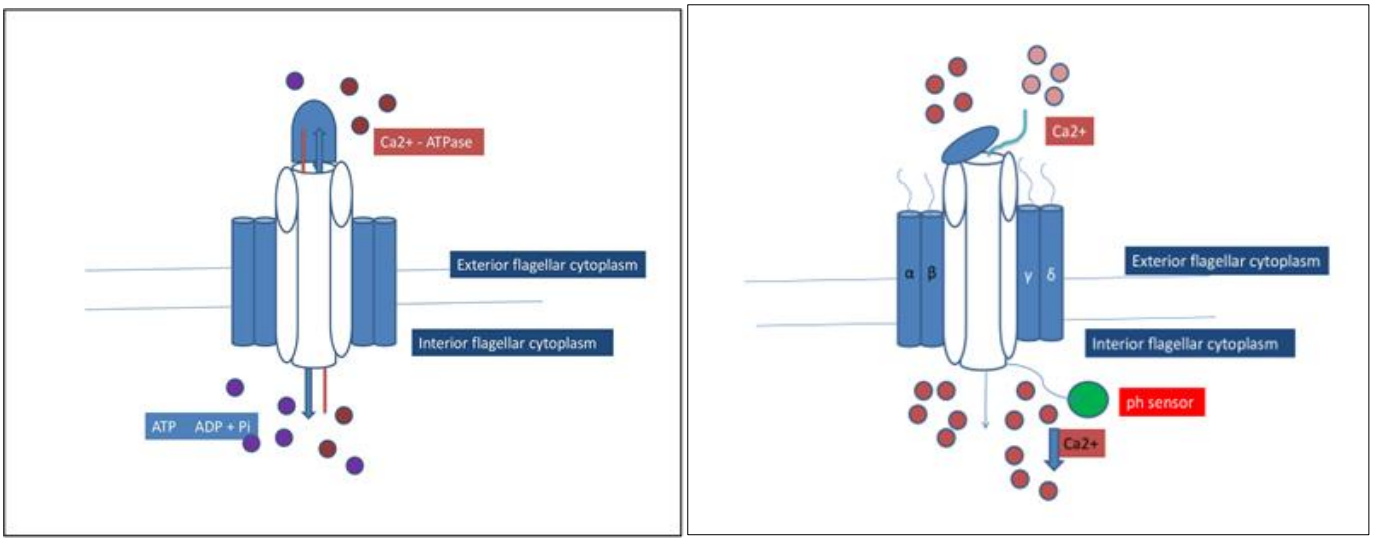

Fig 3: Mode of action of catsper channel

Fig 3 Mode of action of Catsper Channel: Spermatozoa have primarily two flagellar Ca2+ transport proteins that balance the concentration of Ca2+ in the sperm flagellum. Ca2+ ATPase helps pumps Ca2+ out of the spermatozoon and CatSper channel allows the entry of extracellularCa2+ inside the spermatozoon. +-ATPase pumps hydrolyze ATP to export a cytoplasmic Ca2+ions and to import extracellular protons.

Sperm voltage gated proton channels

The proton selective channels were discovered by Thomas and Meech, 1982 [63], although its activity as proton conducting channels were first demonstrated by Sasaki *et al*. 2006 [55] and Ramsey *et al*. 2006 [50]. The proton-selective channel Hv1 (gene name HVCN1 for human or VSOP for mouse) homologous to voltage-sensor domain of the voltage gated cation channel is a four-transmembrane domain protein. Unlike the classical pore conducting channel proton, permeation mainly occurs with a water wire spanning the voltage sensor domain (Ramsey *et al*., 2010) [51]. The Hv1 channel can exists both as a single hv1 subunit and can function independently or as a dimer in the plasma membrane; (Koch *et al*., 2008; Tombola *et al*., 2008) [29, 68]. In 2006 simultaneously two groups Dr.Clapham group (Ramsey *et al*., 2006) [50] identified the presence of proton channels in human and another from Dr. Okumura group confirmed it in mouse and seasquirt genomes (Sasaki *et al*., 2006) [55]. In 2010, direct electrophysiological recordings of human sperm revealed HSper, a strong outwardly rectifying H+ selective current;Hsper is governed by H+ gradients between the intracellular and extra-cellular environments as well as exhibiting an extreme sensitivity to Zn_2^+. The flagellar voltage-gated proton channel Hv1 is the main H^+ extrusion pathway that controls sperm intracellular pH, and the pH-dependent flagellar Ca^{2+} channel. Hv1 and CatSper channels are co-localized within the principal piece of the sperm flagellum and works hand in hand to maintain the pH. Weak bases such as procaine, that require extracellular Ca^{2+} to induce hyperactivation have implicated that pH acts as one of the main components in the signaling pathway that controls Ca^{2+}entry and hyperactivation. Hv1 is dedicated to proton extrusion from flagellum and is activated by membrane depolarization, an alkaline extracellular environment, the endocannabinoid anandamide, and removal of extracellular zinc, a potent Hv1 blocker. Hv1 allows only outward transport of proton. Hv1 is not a true ion channel, but rather a mixture of a transporter and an ion channel without the pore, that provides rapid movement of protons across a lipid bilayer via voltage-gated mechanism. Mishra *et al*., 2019 [43] first

reported the role of Hv1 in regulating sperm motility, capacitation and acrosome reaction in Hariana bull spermatozoa. They suggested that downstream signaling of Hv1 channels activation or inhibition-induced hypermotility is regulated through AC, PKA pathways and Catsper channels were found to be intimately associated with Hv1 function in regulating sperm motility. Proton channels are mostly found at Principal piece of sperm flagellum in humans and mice along with catsper (Lishko *et al*., 2010) [31] (fig 4). A High immunoreactivity was observed at the flagella of bull spermatozoa (Mishra *et al*., 2019) [43] (Fig 4). Although biochemical and functional presence of voltage dependent proton channel in bovine spermatozoa has been suggested by Babcock *et al*., 1983 [3] and Mishra *et al*., 2019 [43] but information about their functional presence and characterization of Hv1 channels in other species other than human and mouse is apparently lacking.

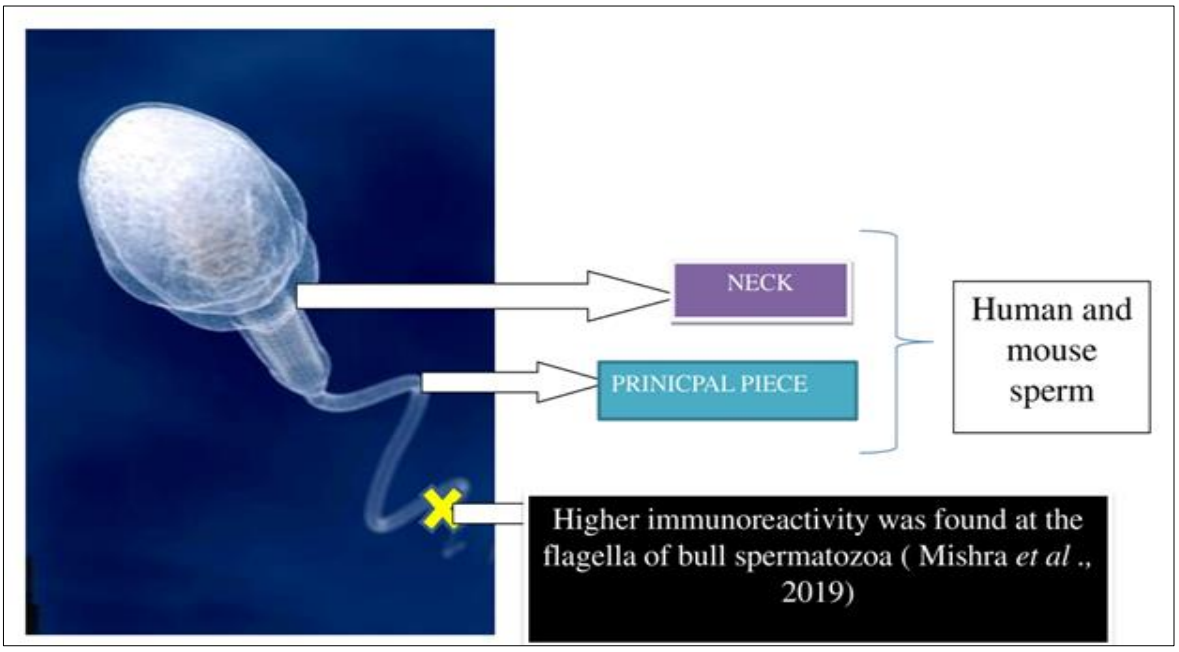

Fig 4: Localization of proton channel

Figure 4: Proton channels are mostly found at Principal piece of sperm flagellum in humans, mice, bull along with catsper

Mode of action of volatage gated proton channel

Mechanism for proton efflux from bovine sperm was via a voltage-gated proton channel was based on the fact that the sperm cytosol becomes alkaline upon membrane depolarization. Bovine sperm flagella are long (60 - 72µm) and maximal percentage of motile sperm were recorded between ph 7.0 and 8.1 for bull (Ho *et al*. 2002) [22]. Motility originates from the flagellum and is powered by adenosine triphosphate (ATP) hydrolysis within the sperm tail (Lishko *et al*., 2016) [35]. ATP generated in the mitochondria in the midpiece takes slightly more time to reach to the end of the flagellum within the extremely narrow flagellum as because diffusion is inversely proportional to the area thorough which it diffuses. Therefore, intraflagellar ATP is generated during glycolysis and oxidative phosphorylation occurs especially at the distal parts of the sperm tail, which results in quick cytoplasm acidification (Lishko *et al*., 2011) [32]. Moreover, axonemal dynein hydrolyzes ATP to produce ADP, Pi, and H+, all of which contributes to intracellular acidification. The prompt removal of protons is thus vital to dynein function. Sperm Hv1 conducts unidirectional transfer of protons much more rapidly and efficiently than do exchangers or transporters to the extracellular space (DeCoursey, *et al*., 2016) [14]. Pumping of Ca^{2+} through Ca^{2+}ATPase and importing of extracellular protons results in acidification of the sperm cytoplasm and to return the system to the functional state, Hv1 may balance ph by proton extrusion (Florman *et al*., 2008) [16]. Hv1 is activated by the combination of the Ph gradient and membrane depolarization. However, because there is always a H^+ gradient out of the spermatozoa, the sperm membrane potential is an important unknown and changes during sperm travel through the female reproductive tract (Sun *et al*., 2017) [62]. Membrane potential is set by Na^+/K^+-ATPases, which distribute ions over long durations, but is rapidly changed by the opening of ion channels (Castillo *et al*., 2015) [9]. Membrane depolarization can also be induced by low micromolar concentrations of the endogenous anandamide produced by cumulus cells that activates sperm Hv1 (Kirchok *et al*., 2011) [27, 28]. There it provides more efficient alkalinization of sperm cytoplasm during sperm penetration through the cumulus oophorus. The effect of anandamide is not mediated by CB1 or CB2 cannabinoid receptors (Lishko *et al*., 2010) [31]. It is more likely to occur through a direct interaction of anandamide with Hv1 (Lishko *et al*., 2010) [31]. The concentration of anandamide present in the fluid of the male and female reproductive tract is present in the nanomolar range. However as because cumulus cells also synthesize and release anandamide, spermatozoa experiences much higher anandamide concentrations during the sperm's penetration of the cumulus oophorus (Gervasi *et al*., 2013) [18]. Hv1 is inhibited by zinc which is mixed with seminal plasma and may prevent premature sperm activation (Lishko *et al*., 2010) [31]. During their travel through the female reproductive pathways, this zinc inhibition is prevented by albumin chelation and absorption by uterine and oviductal epithelium (Lu *et al*., 2008) [40]. The role of sperm-specific Na^+/H^+(sNHE) and $Cl^-/HCO3^-$exchangers are potential mechanisms for intracellular alkalization in ram and rodents

spermatozoon (Muzzachi e*t al.*, 2018: Zeng *et al*., 1996) [44, 72]. NHE is directly responsible for transporting H^+ outside the cell in exchange for extracellular Na^+, its inhibition is supposed to induce proton accumulation inside the cell, thus potentially leading to the inhibition of sperm motility. NHE may function as hyperpolarization activated proton extrusion mechanism since it possesses a putative voltage sensor (Miller *et al*., 2015) [42]. NHE−/−mice were completely infertile due to impaired motility however, they also had unexpectedly low expression of soluble adenylate cyclase (sACY). (Wang *et al*., 2003) [68].

Physiological functions of catsper and proton channels

Sperm hyperactivation is essential for sperm fertility as it enables them to overcome the clutches of the ciliary oviductal epithelium and the protective vestments of the egg for fertilization. If sperm cannot hyperactivate, they are unable to fertilize an egg. Catsper channels play a critical role in hyperactivation and rheotactic response in bull sperm (Johnson *et al*., 2017) [25], boars (Vicente-Carrillo *et al*., 2017) [67] and however rheotactic response was not shown by equine sperm (Loux *et al*., 2014) [38]. Selective Hv1 blockers such as mM2-Guanidinobenzimidazole (2-Guanidinobenzimidazole) resulted in significant reduction in progressive sperm motility (PSM) in bull spermatozoa. Catsper channel blockers such as calcium chelator ethylene glycol tetra-acetic acid, mibefradil, a specific blocker of CatSper channels in human sperm or Catsper1 antibody all significantly inhibited caffeine-induced hyperactivation and the rheotactic response in bull spermatozoa supporting the fact that the calcium influx occurs via CatSper channels and helps regulate hyperactivation and motility (Johnson *et al*., 2017) [25]. After the activation of motility, capacitation is the final maturation of the sperm cells to be able to penetrate and fertilize the egg. The hv1 plays a major role during capacitation by maintaining the proton pump. Treatment with zinc chloride (potent Hv1 blocker) and Anandamide (AEA), an activator of Hv1 resulted in significant increase in B-pattern of spermatozoa indicating induction of capacitation in bull spermatozoa (Mishra *et al*., 2019) [43]. Specific CatSper antagonist such as Mibefradil and NNC 55-0396 effectively blocked CatSper acting as in boar spermatozoa exposed to capacitation inducing media and resulted in reduced sperm motility (Vicentte Carrillo *et al*., 2017).

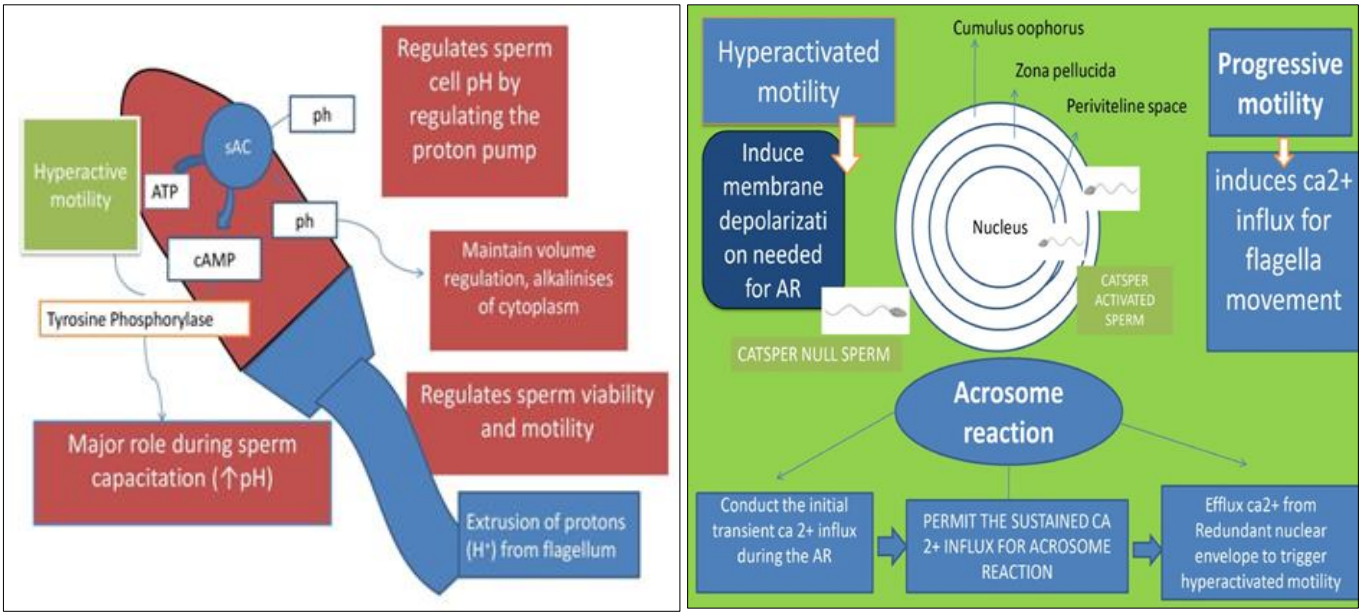

Fig 5: Physiological functions of proton and Catsper channels

Fig 5. Physiological functions of proton and Catsper channels in sperm cell. Proton channels (left figure) plays a major role in capacitation, help regulate sperm cell pH, maintains volume regulation, regulates sperm viability and motility, alkalization of cytoplasm, regulates sperm viability and motility, causes extrusion of protons from flagellum, causes hyperactive motility. Physiological function of catsper channels (Right figure) include hyperactive motility by induction of membrane depolarization needed on acrosome, acrosome reaction, induces ca2+ influx for flagella movement. The figure (right side) suggests how a catsper activated sperm can penetrate a sperm nucleus wherease a catsper null sperm cannot penetrate the sperm nucleus. sAC : soluble adenylcyclase, cAMP – Cyclic adenosine 3,5-monophosphate , ATP – Adenosine monophosphate.

Conclusions

Sperm is the only cell whose activity is outside the male body and inconsistent chemical milieu of sperm, rapid changes during sperm journey to oocyte are dynamically regulated by ion channels. ph plays a significant role in regulating sperm motility and fertility. However, a multimeric approach is required to solve the mysteries behind catsper and proton channels in different species of animals. Understanding ion channels and its role in regulating spermatozoa function will help to develop strategies to treat the basic causes of infertility in animals.

Authors contribution

The authors equally contributed to the preparation and making of the manuscript**.**

Conflict of Interest

There is no conflict of Interest

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