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Review

# Flagellar ion channels of sperm: similarities and differences between species

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ABSTRACT

Motility and fertilization potential of mammalian sperm are regulated by ion homeostasis which in turn is under tight control of ion channels and transporters. Sperm intracellular pH, membrane voltage and calcium concentration ($[Ca^{2+}]_i$) are all important for sperm activity within the female reproductive tract. While all mammalian sperm are united in their goal to find and fertilize an egg, the molecular mechanisms they utilize for this purpose are diverse and differ between species especially on the level of ion channels. Recent direct recording from sperm cells of different species indicate the differences between rodent, non-human primate, ruminant, and human sperm on the basic levels of their ion channel regulation. In this review we summarize the current knowledge about ion channel diversity of the animal kingdom and concentrate our attention on flagellar ion channels of mammalian sperm.


## 1. Introduction

Spermatozoa are remarkable cells, which have fascinated researchers since their early discovery back in the 1677 by Leeuwenhoek [1]. Sperm cells are diverse not only in their morphology but also in terms of the molecular mechanisms that drive their physiology. A spermatozoon is a haploid cell that uses ATP-powered motility to deliver its genetic material to the ovum, depositing the paternal genome to restore diploidy, thus generating an embryo. Sperm cells are terminally differentiated and are thought to be transcriptionally and translationally silent, meaning that spermatozoa are largely unable to synthesize new mRNA or translate it into new polypeptides [2,3]. Mammalian sperm may look morphologically simple, with a single flagellum and head comprised of a condensed nucleus, redundant nuclear envelope and acrosomal vesicle. However, they are equipped with sophisticated molecular mechanisms that allow successful navigation in the female reproductive tract. In addition, mammalian sperm cells vary in size and shape of their head with rodents, such as mouse and rat having a hook-like appearance, and primates or ruminants sharing flat, oval shaped structures (Fig. 1). The molecular mechanisms that allow sperm to successfully navigate the female reproductive tract also vary among species [4,5]. To succeed, a spermatozoon must sense the environment and adapt its motility, which is controlled by ATP production and flagellar ion homeostasis. Sperm intracellular pH, membrane voltage and calcium concentration ($[Ca^{2+}]_i$) are regulated by ion channels and transporters and are vital for sperm survival and fertility [6–33]. In this review we summarize the current knowledge about well-studied sperm ion channels, such as the calcium channel CatSper, proton channel Hv1, potassium channels of the Slo family, as well as recently discovered ion channels of sperm. We also discuss the functional diversity of sperm ion channels among mammalian species(Fig. 2).

## 2. Sperm morphology

Motility originates from the flagellum that is subdivided into three functional parts: mitochondria containing midpiece, a

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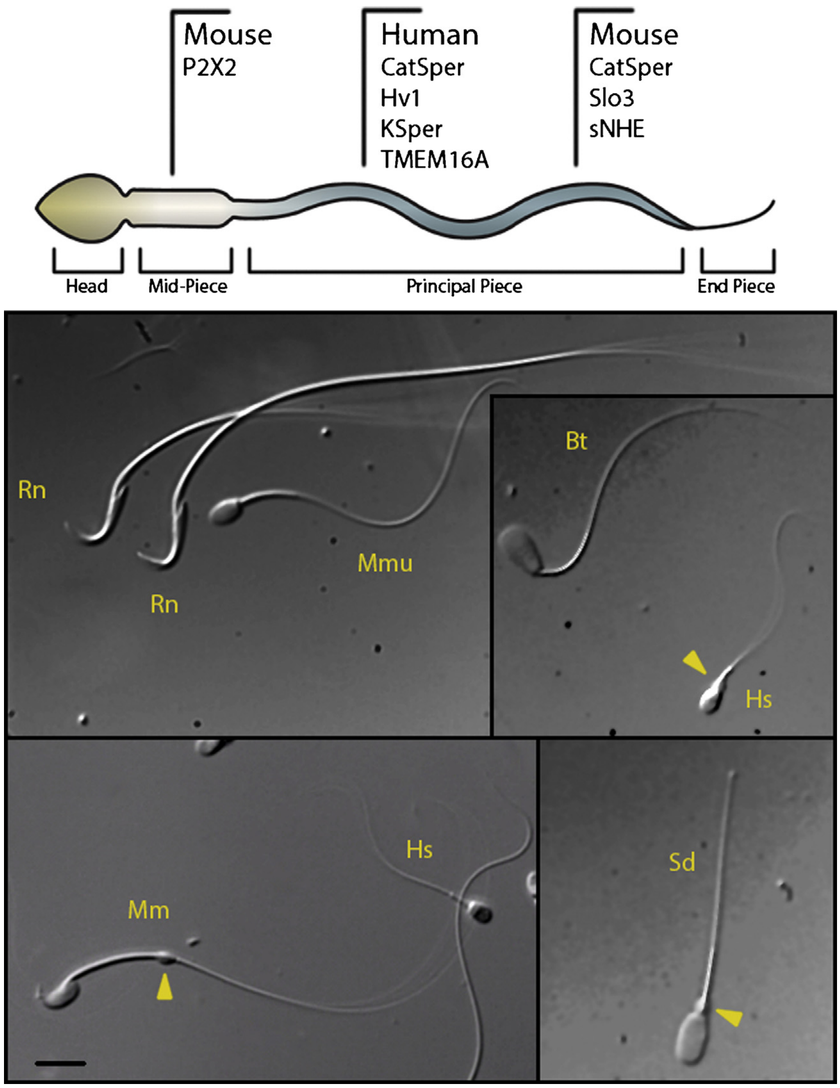


**Fig. 1. Examples of sperm morphological and biochemical diversity.** *Top panel:* schematic representation of spermatozoon with cellular compartments labeled and distribution of species-specific ion channels found within each section. *Bottom panel:* spermatozoa of different species are shown with cytoplasmic droplets indicated by yellow arrows. Shown are: human (Hs; *Homo sapiens*), mouse (Mm; *Mus musculus*), rat (Rn; *Rattus norvegicus*), rhesus macaque (Mmu; *Macaca mulatta*), boar (Sd; *sus scrofa domesticus*), and bull (Bt; *Bos taurus*) sperm cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

principal piece, and the endpiece (Fig. 1, top panel). The flagellum is in essence a motile cilium and is structurally similar in all sperm cells among multiple taxa in that they all have an axoneme with some modifications [34,35]. The flagellar plasma membrane is tightly attached to all underlying structures along the sperm body. This arrangement provides spermatozoa with a ridged structure to which membrane proteins can be tethered to the fibrous sheath [36] to ensure their strict compartmentalization [37]. Many sperm cells possess a single region of the sperm plasma membrane that is loosely attached to the rigid intracellular structures, a so-called cytoplasmic droplet (CD) [38,39]. The CD represents a remnant of the spermatid's cytoplasm and can be located around midpiece, or even more distally on the principal piece. The CD is shed from spermatozoa in certain species upon ejaculation; however, a small number of cells retains it [38,40]. Whether the presence of the CD is an indication of an immature spermatozoon is still questionable, a significant portion of fertile human sperm cells retain this structure. The CD has been proposed to serve as a reservoir for adaption to osmotic stress upon exposure to various environments [38,40–42]. It does however, serve another technical, but useful purpose: the CD allows for formation of tight, gigaohm contact (gigaseal) between sperm membrane and recording electrode which has made sperm patch clamp studies possible [16,43]. While many attempts have been made to study sperm ion channels indirectly [14,44–47], the real breakthrough came after introduction of whole-cell sperm patch clamp method [16,43] which has revolutionized the field of sperm ion channel research. In combination with various genetic models, the sperm patch clamp method provides a particularly useful tool for unbiased study of sperm ion channels of which calcium, potassium, proton, nonselective and various ligand-gated channels have been identified [19,21,48,49].

## 3. Calcium channels and hyperactivation

Calcium signaling is essential for all cell types, sperm being no exception. The maintenance and regulation of intracellular calcium concentration ($[Ca^{2+}]_i$), is therefore, of great importance and is carried out by proteins and co-factors that import, export and/or sequester calcium ions [50]. In spermatozoa, swimming behavior is controlled by rises in $[Ca^{2+}]_i$ that changes flagellar beat pattern through $Ca^{2+}$ sensing proteins calaxins [51,52]. Calcium-bound calaxins inhibit the activity of dynein motors within the