



Flagellar hyperactivation of bull and boar spermatozoa

Harayama, Hiroshi

(Citation)

Reproductive Medicine and Biology, 17(4):442-448

(Issue Date)

2018-10

(Resource Type)

journal article

(Version)

Version of Record

(Rights)

© 2018 The Authors. Reproductive Medicine and Biology published by John Wiley & Sons Australia, Ltd on behalf of Japan Society for Reproductive Medicine.
This is an open access article under the terms of the Creative Commons Attribution - NonCommercial License, which permits use, distribution and reproduction in any mediu...

(URL)

<https://hdl.handle.net/20.500.14094/90006309>



MINI REVIEW

Flagellar hyperactivation of bull and boar spermatozoa

Hiroshi Harayama 

Division of Animal Science, Department of Bioresource Science, Graduate School of Agricultural Science, Kobe University, Kobe, Japan

Correspondence

Laboratory of Reproductive Biology, Division of Animal Science, Department of Bioresource Science, Graduate School of Agricultural Science, Kobe University, 1 Rokkodai, Nada, Kobe, 657-8501, Japan (harayama@kobe-u.ac.jp).

Abstract

Background: In mammals, flagellar hyperactivation is indispensable to sperm fertilization with oocytes in vivo, although there are species differences in regulatory mechanisms for this event. In this study, I reviewed researches regarding hyperactivation of bull and boar spermatozoa, in comparison with those of spermatozoa from other species.

Methods: Recent publications regarding sperm hyperactivation were collected and summarized.

Results (Main findings): In bull and boar spermatozoa, there are two types of hyperactivation “full-type hyperactivation and nonfull-type hyperactivation” which are equivalent to anti-hock hyperactivation and pro-hock hyperactivation of mouse spermatozoa, respectively, on the basis of the flagellar parts exhibiting asymmetrical beating. Full-type hyperactivation is initiated in response to a rapid increase of cytoplasmic Ca^{2+} in the connecting/middle and principal pieces by the mobilization of this divalent ion from extracellular space and internal store through cation channels. Regulatory molecules for the increase of cytoplasmic Ca^{2+} in the connecting/middle pieces are probably different from those in the principal pieces.

Conclusion: I have proposed a hypothesis on the regulation of full-type hyperactivation by the distinct signaling cascades leading to the increase in cytoplasmic Ca^{2+} between the connecting/middle and principal pieces of bull and boar spermatozoa.

KEYWORDS

Ca^{2+} , capacitation, hyperactivated movement, livestock, sperm

1 | INTRODUCTION

In mammals, freshly ejaculated spermatozoa can exhibit intensive and progressive movement but cannot fertilize oocytes immediately. After staying under the special environment of female reproductive tract for a certain period (more than several hours for bull and boar spermatozoa), they become capable of accomplishing fertilization with oocytes.¹ This event is called “capacitation” which was discovered independently by Dr Chang^{2,3} and Dr Austin in 1951.^{4,5} Capacitation is currently defined as sequential and various changes of spermatozoa within female reproductive tracts.^{1,3,6} One of the

changes which are observed during early stage of capacitation is release of decapacitation factors from sperm surface. So far, surface coating proteins (eg acrosomal stabilizing factor and seminal vesicle secretions)^{7–9} and lipids (eg cholesterol),¹⁰ which stabilize sperm membranes, have been identified as decapacitation factors. As explained previously,⁹ seminal vesicle secretion 2 (SVS2) is one of major proteins secreted from mouse seminal vesicle and exposed to spermatozoa at ejaculation. In the uterus, SVS2 attaches to spermatozoa via the plasma membrane ganglioside GM1 probably in order to protect sterols (including cholesterol) in the sperm plasma membrane. In the oviduct, however, this protectant (SVS2) of the sterols (including

cholesterol) detaches from the sperm plasma membrane, thereby increasing chances of cholesterol release from the spermatozoa. Thus, SVS2 may suppress sperm ectopic capacitation (precocious capacitation) in the uterus. This is consistent with the observation that sperm capacitation progresses faster in the oviductal isthmus.¹ Moreover, for the release of cholesterol from the plasma membrane, this lipid need be externalized by the actions of oxysterols (cholesterols oxidized by reactive oxygen species)^{11,12} and plasma membrane scramblases (which translocate phospholipids between outer and inner lipid layers of the plasma membrane)^{13,14} and then need become water soluble by the conjugation with its acceptors (albumin-like proteins) of female reproductive fluids.^{10,11}

Activation of the intracellular cyclic adenosine monophosphate (cAMP) signaling cascades and consequent protein phosphorylation play pivotal roles in the regulation of capacitation process in mammalian spermatozoa. Specifically, spermatozoa are exposed to bicarbonate (HCO_3^-) of fluids of male and female reproductive tracts at ejaculation. HCO_3^- is transported into the sperm cytoplasm through ion transporters of the plasma membrane (sodium-bicarbonate co-transporter and bicarbonate-chloride antiporter) and subsequently binds to adenylyl cyclase 10 (ADCY10, it is also called soluble adenylyl cyclase). In response to HCO_3^- , ADCY10 actively converts adenosine triphosphates (ATP) to cAMP.^{15–17} The increased cAMP can activate a main target molecule “protein kinase A (PKA)” that is localized in the flagella by the interaction between A-kinase anchoring protein (AKAP) and PKA regulatory subunits. Such increases of the cytoplasmic cAMP and activation of PKA occur during the early stage of capacitation.^{16,18,19} Moreover, the cAMP/PKA-dependent signaling cascades may be linked to the intracellular changes which allow spermatozoa to undergo the influx of extracellular Ca^{2+} and recruitment of Ca^{2+} from the internal store (redundant nuclear envelope of the connecting piece) during the late stage of capacitation. These changes include functionalization of Ca^{2+} channels (voltage-dependent Ca^{2+} channel, VDCC) by the plasma membrane hyperpolarization and cytoplasmic alkalization, and accumulation of cytoplasmic ligands (inositol 1,4,5-trisphosphate, IP_3) for ligand-gated Ca^{2+} channels (IP_3 receptor, IP_3R). After accomplishment of these capacitation-related changes, ion gates of the above-mentioned Ca^{2+} channels can be opened in response to proper stimuli (eg plasma membrane depolarization and interaction with the ligands) or spontaneously, and resultant increases of cytoplasmic Ca^{2+} allow the spermatozoa to initiate hyperactivation in the flagella.^{20–22} However, details of the linkage of cAMP/PKA-dependent signaling cascades with the increase in the intracellular Ca^{2+} remain to be fully understood, especially in the context of species differences.

There are a number of differences in sperm characteristics among the primate (humans), livestock (eg bulls and boars), and laboratory animal (eg mice, rats and hamsters), including the shape of head, length of flagellum, structural robustness, metabolic system, molecular composition of plasma membrane, and molecules for the intracellular signal transduction.^{1,16,23,24} Thus, it is necessary to make detailed researches on the interspecies differences in the sperm functions in order to elucidate mechanisms for the expression

of fertilizing ability in mammalian spermatozoa. According to our previous investigations of bull and boar spermatozoa,^{25–29} ADCY10 and PKA are localized in the specific subcellular segments including the connecting and principal pieces, and proteins are preferentially phosphorylated in these segments of the spermatozoa treated with the cAMP analog to induce capacitation-related events leading to hyperactivation. These results are consistent with our hypothesis that connecting pieces of bull and boar spermatozoa have unique cAMP-dependent controllers for regulation of the capacitation-related events leading to hyperactivation.^{16,28} In this study, I described current status of researches on flagellar hyperactivation of bull and boar spermatozoa, in comparison with those of the spermatozoa from other species.

2 | ROLES AND CHARACTERISTICS OF FLAGELLAR HYPERACTIVATION

2.1 | Hyperactivation in female reproductive tract

Mammalian spermatozoa can initiate flagellar movement with whip-lash-like beating and large amplitude during staying at female reproductive tract.^{30–32} This pattern of flagellar movement is termed “hyperactivation” that was first observed by Professor Yanagimachi of Hawaii University in hamster spermatozoa.^{33–35} It has generally been considered that hyperactivation yields stronger driving force that enables capacitated spermatozoa to leave the epithelia of oviductal isthmus, migrate to the oviductal ampulla, and penetrate the cumulus oophorus and zona pellucida of oocytes.^{1,36,37} In addition, accomplishment of capacitation-related events in the flagella is essential to the occurrence of hyperactivation.^{6,16} Although the site of female reproductive tract in which spermatozoa initiate capacitation-related events may be different among species, almost parts of capacitation are accomplished in the oviductal isthmus (sperm reservoir) where fertilizing spermatozoa are stored.¹ These indicate that occurrence of in-vivo hyperactivation may be modulated by the interaction between spermatozoa and oviductal isthmus.

2.2 | Induction of hyperactivation in vitro

In mouse and hamster epididymal spermatozoa, hyperactivation can be induced highly in vitro by incubation in a capacitation-supporting medium, including HCO_3^- , Ca^{2+} , and cholesterol acceptors.^{38–41} Researches with hamster epididymal spermatozoa proposed that occurrence of hyperactivation is hastened or delayed by the interaction with specific fluid components of female reproductive tracts, such as progesterone, 17β -estradiol, melatonin, serotonin and γ -aminobutyric acid, probably in order to modulate the timing of arrival of capacitated/acrosome-reacted spermatozoa at the oviductal ampulla where ovulated oocytes are ready for the fertilization.^{42,43} In bull and boar ejaculated spermatozoa, by contrast, it may be difficult to induce hyperactivation highly by the simple incubation in the capacitation-supporting medium.^{44–47} This suggests existence of

strong suppressors (eg a calyculin-sensitive protein phosphatase) for hyperactivation in the spermatozoa from livestock.²⁸ Instead, hyperactivation can be induced highly in the uncapacitated spermatozoa in vitro by the treatment with the elevators of the intracellular Ca^{2+} level [eg A23187 (extracellular Ca^{2+} -dependent hyperactivation) and thimerosal (extracellular Ca^{2+} -independent hyperactivation)], although the activation of the intracellular cAMP-PKA signaling cascades is perhaps skipped in these spermatozoa.^{48–51} In our laboratory,^{28,51,52} extracellular Ca^{2+} -dependent hyperactivation can be induced highly in bull and boar ejaculated spermatozoa by the treatment with the cell-permeable cAMP analog to stimulate the intracellular cAMP-PKA signaling cascades. Specifically, replacement of NaHCO_3 (an activator of ADCY10) with a cell-permeable, phosphodiesterase-resistant cAMP analog (Sp-5,6-dichloro-1- β -D-ribofuranosyl-benzimidazole-3',5'-cyclic monophosphorothioate, cBiMPS), and supplementation of an inhibitor for protein phosphatase 1 and protein phosphatase 2A (calyculin A) dramatically improved the capacity of the capacitation-supporting medium to induce hyperactivation in bull and boar ejaculated spermatozoa.^{28,53} These indicate that species-specific parts of the intracellular cAMP/protein phosphorylation-dependent signaling cascades are suppressed more strongly in bull and boar ejaculated spermatozoa than in mouse and hamster epididymal spermatozoa.

2.3 | Movement patterns of hyperactivation

As parts of flagellum in which bull and boar hyperactivated spermatozoa exhibit asymmetrical beating with large amplitude are varied among cells, hyperactivation is classified into two types “nonfull type” and “full type” in our laboratory (Figure 1, Movie S1).^{28,44,54} Specifically, the whole part of middle and principal pieces repeats asymmetrical and large beatings in the full-type hyperactivated spermatozoa. The angel of bending of the upper part of middle piece (especially near the connecting piece) is apparently larger in boar spermatozoa than bull spermatozoa. Full-type hyperactivated spermatozoa of the bull exhibit twisting movement/figure eight-like movement in the nonviscous medium, and they crawl progressively in the viscous medium.²⁸ On the other hand, asymmetrical and large beatings of nonfull-type hyperactivated spermatozoa are limited to the lower part of middle piece and whole part of principal piece, and the upper part of middle piece are relatively quiet. Nonfull-type hyperactivated spermatozoa of the bull are likely to exhibit round movement with the counterclockwise circling direction, when they are observed under the upright microscope (Movie S1). Very recently, we also found that almost of bull uncapacitated spermatozoa suspended in the medium without HCO_3^- , Ca^{2+} , and cholesterol acceptors exhibit similar round movement with the preferential circling direction which is clockwise (when observing sperm samples using the upright microscope).⁵⁵ This is in agreement with the previous observation using bull frozen-thawed spermatozoa (round movement with the preferential counterclockwise direction when observing sperm samples using the inverted microscope).⁵⁶ These suggest that observations of the circling direction may enable

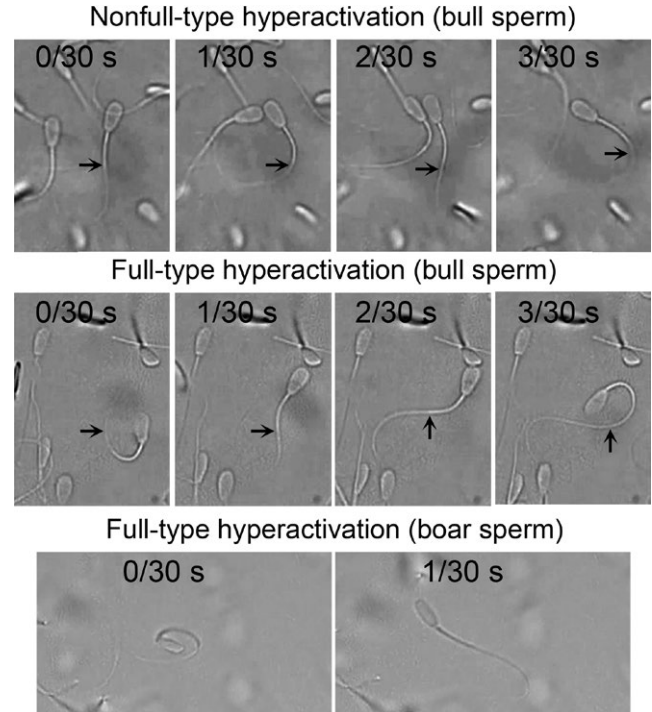


FIGURE 1 Flagellar movement patterns of nonfull-type or full-type hyperactivated spermatozoa from livestock. Bull and boar ejaculated spermatozoa were washed and incubated to induce hyperactivation as described in our previous reports.^{28,54} Microscopic movies of them were captured and divided into frames of JPEG images. Arrows indicate typical examples of flagellar movement patterns. Frame rate was 30 Hz. Photos of the spermatozoa were re-used in this study with the permission of Japanese Journal of Embryo Transfer

to classify round movement into nonfull-type hyperactivation and uncapacitated sperm movement in the motility assessment of bull ejaculated spermatozoa.

In mouse epididymal spermatozoa which have longer flagella than bull and boar ejaculated spermatozoa, there are also two types of hyperactivation. They are called pro-hock hyperactivation and anti-hock hyperactivation, which are probably equivalent to nonfull-type hyperactivation and full-type hyperactivation of bull and boar ejaculated spermatozoa, respectively, on the basis of the flagellar parts exhibiting asymmetrical beatings and sperm movement patterns in the nonviscous medium.^{38,40} Moreover, as almost of mouse ejaculated spermatozoa exhibit anti-hock hyperactivation in the oviduct,³² it has been considered that in vivo-hyperactivated spermatozoa may exhibit asymmetrical and large beatings in the whole parts of middle and principal pieces. Movement trajectories of mouse hyperactivated spermatozoa suspended in the viscous medium are considerably straighter than those in the nonviscous medium,⁵⁷ indicating in vivo-hyperactivated spermatozoa are able to move in a forward direction through viscous fluids of female reproductive tracts. In hamster epididymal spermatozoa which have longer flagella than mouse spermatozoa, antisymmetrisation of the beating and enlargement of the amplitude are also observed in the flagella at

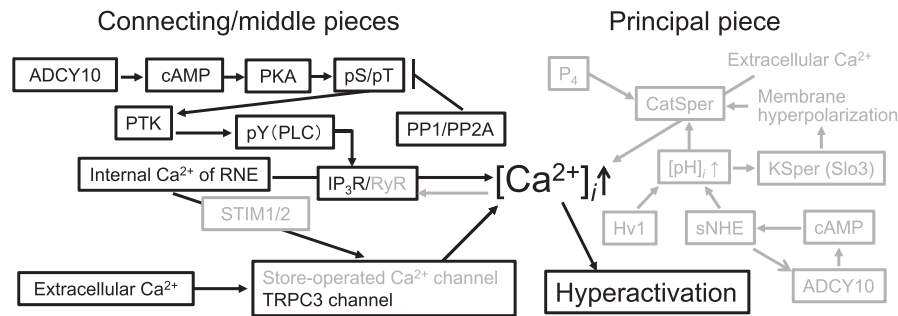


FIGURE 2 A working hypothesis on the regulation of full-type hyperactivation by the distinct signaling cascades between the connecting/middle and principal pieces of bull and boar ejaculated spermatozoa. Gray-colored molecules and events are based on the information obtained in spermatozoa from other species. ADCY10: adenyl cyclase 10, cAMP: cyclic adenosine monophosphate, PKA: protein kinase A, pS/pT: protein phosphorylation at serine/threonine residues, PP1/PP2A: protein phosphatase 1/protein phosphatase 2A, PTK: protein tyrosine kinase, pY: protein phosphorylation at tyrosine residues, PLC: phospholipase C, RNE: redundant nuclear envelope of the connecting piece (Ca^{2+} store), IP_3R : inositol 1,4,5-trisphosphate receptor, RyR: ryanodine receptor, STIM: stromal interaction molecule, TRPC3: transient receptor potential cation channel subfamily C member 3, Hv: voltage-dependent H^+ channel, sNHE: sperm specific Na^+/H^+ exchanger

the occurrence of hyperactivation. However, a recent article claimed that they symmetrize flagellar beating with the large amplitude at the late stage of hyperactivation, and exhibit figure eight-like movement in the nonviscous medium.⁵⁸ As this finding is very interesting, it is necessary to investigate whether such symmetrization of the flagellar beating occurs in bull and boar spermatozoa at the late stage of hyperactivation.

3 | REGULATORY MECHANISMS FOR FLAGELLAR HYPERACTIVATION

3.1 | Ca^{2+} as an initiator of hyperactivation

Occurrence of sperm hyperactivation requires two major changes “antisymmetrisation of flagellar beating” and “enlargement of beating amplitude.” Brokaw⁵⁹ showed Ca^{2+} is an initial promoter for the antisymmetrization of flagellar beating in detergent-demembranated sea urchin spermatozoa. Suarez and her colleagues also confirmed that Ca^{2+} can antisymmetrize flagellar bending by increasing the curvatures of the principal bend in detergent-demembranated bull spermatozoa.⁶⁰ Moreover, the treatment with the elevators of the intracellular Ca^{2+} level can induce hyperactivation rapidly and highly in the uncapacitated spermatozoa in vitro.^{48–51} These results have established a current theory that the most important initiator of hyperactivation is a rapid increase of cytoplasmic Ca^{2+} that is induced by the influx from extracellular space and recruitment from the internal store.^{20,37,61}

3.2 | Ca^{2+} channel

Mammalian spermatozoa possess at least three types of Ca^{2+} channels, including VDCC, ligand-gated Ca^{2+} channel (IP_3R), and store-operated Ca^{2+} channel (SOC).^{20,62} In mouse capacitated spermatozoa, CatSper channel is sperm-specific VDCC with the pH sensor, localized in the principal pieces, and activated and gated by

the detection of capacitation-related alkalization of the cytoplasm and changes of membrane potentials. This special channel has currently been considered to mediate the influx of sufficient Ca^{2+} for the trigger of hyperactivation.⁶³ In fact, male CatSper-KO mice and men with mutations in CATSPER genes are infertile.^{64,65} Epididymal spermatozoa from male CatSper-KO mice are incapable of exhibiting hyperactivation by incubation in the capacitation-supporting medium.^{64,66,67} Although the CatSper channels exist in bull and boar ejaculated spermatozoa,^{68,69} further experiments are necessary to demonstrate their functions in the occurrence of hyperactivation.

In bulls, boars, and mice, hyperactivation can be induced immediately in uncapacitated spermatozoa by a short treatment with putative stimulator for IP_3R “thimerosal.” The thimerosal-induced hyperactivation is full-type (bulls and boars)/anti-hock (mice).^{38,50,51,70} Moreover, indirect immunofluorescence and ultrastructural observations indicate existence of the internal store with IP_3R in the redundant nuclear envelope (RNE) of the connecting piece.^{71,72} These are consistent with the suggestions that ligand-gated Ca^{2+} channel “ IP_3R ” of RNE is involved in the initiation of full-type/anti-hock hyperactivation, and that sufficient Ca^{2+} for the trigger of full-type/anti-hock hyperactivation can be supplied solely from RNE. Under the physiological condition, IP_3R of RNE may be gated by the interaction with the ligands that may be generated by phospholipase C during sperm capacitation, and consequently released Ca^{2+} promotes the antisymmetrization of flagellar beating, especially in the middle piece. However, it should be noted that the thimerosal-induced hyperactivation is not sustainable and suggests functions of other Ca^{2+} channels may be required for the maintenance of full-type/anti-hock hyperactivation. In human spermatozoa, ryanodine receptor (RyR) is likely to mediate the recruitment of cytoplasmic Ca^{2+} from RNE in a manner of calcium-induced calcium release (CICR) and potentially regulates the occurrence of hyperactivation,⁷³ although existence and functions of RyR still remain to be revealed in bull and boar ejaculated spermatozoa. Furthermore, we recently reported that the other Ca^{2+} channel “transient receptor potential cation channel subfamily C member 3, TRPC3” is present in

the connecting and middle pieces of boar ejaculated spermatozoa and involved in the extracellular Ca^{2+} -dependent occurrence of full-type hyperactivation after preincubation with cAMP analog.⁵¹ At least in boar ejaculated spermatozoa, TRPC3 channel may mediate the cAMP signaling-dependent influx of extracellular Ca^{2+} leading to full-type hyperactivation. In marine invertebrates, additionally, several kinds of Ca^{2+} channels mediate the influx of extracellular Ca^{2+} , and SOC of ascidian spermatozoa is involved in the antisymmetrisation of flagellar beating.⁷⁴

3.3 | Intracellular signaling cascades that are activated by the increase of cytoplasmic Ca^{2+}

There are a number of unclear points regarding the signal transduction systems between the increase of cytoplasmic Ca^{2+} and initiation of hyperactivation in bull and boar spermatozoa. For instance, functions of the conventional mediators “calmodulin (CaM) and CaM-dependent kinases” are still controversial.^{53,75} Although calpain 2 of boar spermatozoa is involved in the intracellular Ca^{2+} signal cascades leading to full-type hyperactivation,⁵⁴ detailed roles of this Ca^{2+} -dependent protease still remain unclear. However, reports regarding spermatozoa from other species have proposed several hyperactivation-associated molecules that can react to the increase of cytoplasmic Ca^{2+} , including protein phosphatase 2B (calcineurin),⁷⁶ F-actin,⁷⁷ and calaxin.^{78–80} In particular, calaxin is indispensable to the Ca^{2+} -dependent antisymmetrisation of flagellar bending and directly decelerates the sliding of microtubules in ascidian spermatozoa. Meanwhile, a treatment with A23187 rescues the ability to fertilize oocytes (including the capacity to undergo hyperactivation) in spermatozoa from infertile *CatSper1*-, *Adcy10*-, or *Ksper* (*Slo3*)-KO mice, but does not recover it in spermatozoa from infertile *Pmaca* (Ca^{2+} efflux pump on the plasma membrane)-KO mice, suggesting importance of a transient increase in cytoplasmic Ca^{2+} in the expression of fertilizing ability including the ability to undergo hyperactivation.⁸¹ Thus, it may be also necessary to focus on roles of the clearance of cytoplasmic Ca^{2+} in the occurrence of hyperactivation.

4 | CONCLUSION

In this study, I reviewed researches on flagellar hyperactivation of bull and boar spermatozoa, in comparison with those of spermatozoa from other species. Based on the accumulated knowledge, I have proposed a working hypothesis regarding regulation of full-type hyperactivation by the distinct signaling cascades between the connecting/middle and principal pieces of bull and boar ejaculated spermatozoa (Figure 2). Specifically, full-type hyperactivation requires an influx of extracellular Ca^{2+} as well as recruitment of stored Ca^{2+} in the connecting/middle pieces in response to up-regulation of the cAMP/PKA-dependent signaling activity. Moreover, an influx of extracellular Ca^{2+} in the principal piece is probably required for

full-type (anti-hock) hyperactivation, although information on the signaling molecules are available only on the spermatozoa from the other species (gray-colored molecules of Figure 2).^{20,22,82} However, only limited data are reported on the signaling molecules between the increase of cytoplasmic Ca^{2+} and initiation of full-type hyperactivation. In order to elucidate mechanisms for full-type hyperactivation in bull and boar spermatozoa, further researches should be made on the signaling molecules that are localized in the principal piece and Ca^{2+} -dependently activated in the flagella.

ACKNOWLEDGEMENTS

I am grateful to Dr. Moriyuki Fukushima, Dr. Osamu Shidara, Dr. Mitsuhiro Sakase (Hokubu Agricultural Institute, Hyogo Prefectural Technology Center for Agriculture, Forestry and Fisheries), and students and staffs of our laboratory for their significant contribution to our research projects.

ETHICAL APPROVAL

Human studies: This article does not contain any studies with human subjects performed by the author.

An animal use ethics statement: No animal experiment was performed for the contribution of this review article.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ORCID

Hiroshi Harayama  <http://orcid.org/0000-0003-0583-8497>

REFERENCES

1. Yanagimachi R. Mammalian fertilization. In: Knobil E, Neill JD, eds. *The Physiology of Reproduction*, 2nd edn. New York, NY: Raven Press; 1994:189-317.
2. Chang MC. Fertilizing capacity of spermatozoa deposited into the fallopian tubes. *Nature*. 1951;168:697-698.
3. Gervasi MG, Visconti PE. Chang's meaning of capacitation: a molecular perspective. *Mol Reprod Dev*. 2016;83:860-874.
4. Austin CR. Observations on the penetration of the sperm in the mammalian egg. *Aust J Sci Res B*. 1951;4:581-596.
5. Austin CR. The capacitation of the mammalian sperm. *Nature*. 1952;170:326.
6. Aitken RJ, Nixon B. Sperm capacitation: a distant landscape glimpsed but unexplored. *Mol Hum Reprod*. 2013;19:785-793.
7. Oliphant G, Reynolds AB, Thomas TS. Sperm surface components involved in the control of the acrosome reaction. *Am J Anat*. 1985;174:269-283.
8. Kuo YW, Li SH, Maeda K, Gadella BM, Tsai PS. Roles of the reproductive tract in modifications of the sperm membrane surface. *J Reprod Dev*. 2016;62:337-343.
9. Araki N, Trencsényi G, Krasznai ZT et al. Seminal vesicle secretion 2 acts as a protectant of sperm sterols and prevents ectopic sperm capacitation in mice. *Biol Reprod*. 2015;92:8.

10. Cross NL. Role of cholesterol in sperm capacitation. *Biol Reprod.* 1998;59:7-11.
11. Gadella BM, Boerke A. An update on post-ejaculatory remodeling of the sperm surface before mammalian fertilization. *Theriogenology.* 2016;85:113-124.
12. Aitken RJ, Baker MA, Nixon B. Are sperm capacitation and apoptosis the opposite ends of a continuum driven by oxidative stress? *Asian J Androl.* 2015;17:633-639.
13. Flesch FM, Brouwers JF, Nievelstein PF et al. Bicarbonate stimulated phospholipid scrambling induces cholesterol redistribution and enables cholesterol depletion in the sperm plasma membrane. *J Cell Sci.* 2001;114:3543-3555.
14. Harrison RA, Gadella BM. Bicarbonate-induced membrane processing in sperm capacitation. *Theriogenology.* 2005;63:342-351.
15. Okamura N, Tajima Y, Soejima A, Masuda H, Sugita Y. Sodium bicarbonate in seminal plasma stimulates the motility of mammalian spermatozoa through direct activation of adenylate cyclase. *J Biol Chem.* 1985;260:9699-9705.
16. Harayama H. Roles of intracellular cyclic AMP signal transduction in the capacitation and subsequent hyperactivation of mouse and boar spermatozoa. *J Reprod Dev.* 2013;59:421-430.
17. Buffone MG, Wertheimer EV, Visconti PE, Krapf D. Central role of soluble adenylyl cyclase and cAMP in sperm physiology. *Biochim Biophys Acta.* 2014;1842:2610-2620.
18. Harrison RA. Rapid PKA-catalysed phosphorylation of boar sperm proteins induced by the capacitating agent bicarbonate. *Mol Reprod Dev.* 2004;67:337-352.
19. Visconti PE. Understanding the molecular basis of sperm capacitation through kinase design. *Proc Natl Acad Sci USA.* 2009;106:667-668.
20. Darszon A, Nishigaki T, Wood C, Treviño CL, Felix R, Beltrán C. Calcium channels and Ca^{2+} fluctuations in sperm physiology. *Int Rev Cytol.* 2005;243:79-172.
21. Visconti PE, Krapf D, de la Vega-Beltrán JL, Acevedo JJ, Darszon A. Ion channels, phosphorylation and mammalian sperm capacitation. *Asian J Androl.* 2011;13:395-405.
22. Darszon A, Sánchez-Cárdenas C, Orta G et al. Are TRP channels involved in sperm development and function? *Cell Tissue Res.* 2012;349:749-764.
23. Eddy EM. The spermatozoon. In: Neill JD, ed. *Knobil and Neill's Physiology of Reproduction*, 3rd edn. St. Louis, MO: Elsevier Academic Press; 2006:3-54.
24. Goto N, Harayama H. Calyculin A-sensitive protein phosphatases are involved in maintenance of progressive movement in mouse spermatozoa in vitro by suppression of autophosphorylation of protein kinase A. *J Reprod Dev.* 2009;55:327-334.
25. Harayama H, Nakamura K. Changes of PKA and PDK1 in the principal piece of boar spermatozoa treated with a cell-permeable cAMP analog to induce flagellar hyperactivation. *Mol Reprod Dev.* 2008;75:1396-1407.
26. Tate S, Nakamura K, Suzuki C, Noda T, Lee J, Harayama H. Evidence of the existence of adenylyl cyclase 10 (ADCY10) ortholog proteins in the heads and connecting pieces of boar spermatozoa. *J Reprod Dev.* 2010;56:271-278.
27. Noda T, Sakase M, Fukushima M, Harayama H. Novel approach for the detection of the vestiges of testicular mRNA splicing errors in mature spermatozoa of Japanese black bulls. *PLoS One.* 2013;8:e57296.
28. Mizuno Y, Isono A, Kojima A et al. Distinct segment-specific functions of calyculin A-sensitive protein phosphatases in the regulation of cAMP-triggered events in ejaculated bull spermatozoa. *Mol Reprod Dev.* 2015;82:232-250.
29. Harayama H, Minami K, Kishida K, Noda T. Protein biomarkers for male artificial insemination subfertility in bovine spermatozoa. *Reprod Med Biol.* 2017;16:89-98.
30. Suarez SS, Dai XB, DeMott RP, Redfern K, Mirando MA. Movement characteristics of boar sperm obtained from the oviduct or hyperactivated in vitro. *J Androl.* 1992;13:75-80.
31. Suarez SS, Osman RA. Initiation of hyperactivated flagellar bending in mouse sperm within the female reproductive tract. *Biol Reprod.* 1987;36:1191-1198.
32. Chang H, Suarez SS. Unexpected flagellar movement patterns and epithelial binding behavior of mouse sperm in the oviduct. *Biol Reprod.* 2012;86:140.
33. Yanagimachi R. The movement of golden hamster spermatozoa before and after capacitation. *J Reprod Fertil.* 1970;23:193-196.
34. Yanagimachi R. Mechanisms of fertilization in mammals. In: Mastroianni L, Biggers JD, eds. *Fertilization and Embryonic Development In Vitro*. New York, NY: Plenum Press; 1981:81-182.
35. Yanagimachi R. Germ cell research: a personal perspective. *Biol Reprod.* 2009;80:204-218.
36. Suarez S. Hyperactivated motility of sperm. *J Androl.* 1996;17:331-335.
37. Suarez SS. Control of hyperactivation in sperm. *Hum Reprod Update.* 2008;14:647-657.
38. Chang H, Suarez SS. Two distinct Ca^{2+} signaling pathways modulate sperm flagellar beating patterns in mice. *Biol Reprod.* 2011;85:296-305.
39. Tateno H, Krapf D, Hino T et al. Ca^{2+} ionophore A23187 can make mouse spermatozoa capable of fertilizing in vitro without activation of cAMP-dependent phosphorylation pathways. *Proc Natl Acad Sci USA.* 2013;110:18543-18548.
40. Li H, Hung PH, Suarez SS. Ejaculated mouse sperm enter cumulus-oocyte complexes more efficiently in vitro than epididymal sperm. *PLoS One.* 2015;10:e0127753.
41. Suzuki T, Fujinoki M, Shibahara H, Suzuki M. Regulation of hyperactivation by PPP2 in hamster spermatozoa. *Reproduction.* 2010;139:847-856.
42. Fujinoki M, Takei GL, Kon H. Non-genomic regulation and disruption of spermatozoal in vitro hyperactivation by oviductal hormones. *J Physiol Sci.* 2016;66:207-212.
43. Fujinoki M, Takei GL. γ -Aminobutyric acid suppresses enhancement of hamster sperm hyperactivation by 5-hydroxytryptamine. *J Reprod Dev.* 2017;63:67-74.
44. Harayama H, Mizuno Y. Current status of researches on sperm flagellar hyperactivation in livestock. *Jpn J Embryo Transfer.* 2017;39:159-167 [in Japanese].
45. Marquez B, Suarez SS. Different signaling pathways in bovine sperm regulate capacitation and hyperactivation. *Biol Reprod.* 2004;70:1626-1633.
46. Umezu K, Hiradate Y, Oikawa T et al. Exogenous neurotensin modulates sperm function in Japanese black cattle. *J Reprod Dev.* 2016;62:409-414.
47. Katoh Y, Takebayashi K, Kikuchi A et al. Porcine sperm capacitation involves tyrosine phosphorylation and activation of aldose reductase. *Reproduction.* 2014;148:389-401.
48. Tateno H, Mikamo K. A chromosomal method to distinguish between X- and Y-bearing spermatozoa of the bull in zona-free hamster ova. *J Reprod Fertil.* 1987;81:119-125.
49. Schmidt H, Kamp G. Induced hyperactivity in boar spermatozoa and its evaluation by computer-assisted sperm analysis. *Reproduction.* 2004;128:171-179.
50. Ho HC, Suarez SS. An inositol 1,4,5-trisphosphate receptor-gated intracellular Ca^{2+} store is involved in regulating sperm hyperactivated motility. *Biol Reprod.* 2001;65:1606-1615.
51. Otsuka N, Harayama H. Characterization of extracellular Ca^{2+} -dependent full-type hyperactivation in ejaculated boar spermatozoa preincubated with a cAMP analog. *Mol Reprod Dev.* 2017;84:1203-1217.

52. Harayama H, Miyake M. A cyclic adenosine 3',5'-monophosphate-dependent protein kinase C activation is involved in the hyperactivation of boar spermatozoa. *Mol Reprod Dev.* 2006;73:1169-1178.
53. Harayama H, Noda T, Ishikawa S, Shidara O. Relationship between cyclic AMP-dependent protein tyrosine phosphorylation and extracellular calcium during hyperactivation of boar spermatozoa. *Mol Reprod Dev.* 2012;79:727-739.
54. Kojima A, Matsushita Y, Ogura Y et al. Roles of extracellular Ca^{2+} in the occurrence of full-type hyperactivation in boar ejaculated spermatozoa pre-incubated to induce the cAMP-triggered events. *Andrology.* 2015;3:321-331.
55. Yamada A, Sakase M, Fukushima M, Harayama H Reconsideration of the evaluation criteria for bull ejaculated sperm motility in the context of rotation. *J Reprod Dev.* 2018; in press. <https://doi.org/10.1262/jrd.2018-036>.
56. Nosrati R, Driouchi A, Yip CM, Sinton D. Two-dimensional slither swimming of sperm within a micrometre of a surface. *Nat Commun.* 2015;6:8703.
57. Suarez SS, Katz DF, Owen DH, Andrew JB, Powell RL. Evidence for the function of hyperactivated motility in sperm. *Biol Reprod.* 1991;44:375-381.
58. Takei GL, Fujinoki M, Yoshida K, Ishijima S. Regulatory mechanisms of sperm flagellar motility by metachronal and synchronous sliding of doublet microtubules. *Mol Hum Reprod.* 2017;23:817-826.
59. Brokaw CJ. Calcium-induced asymmetrical beating of triton-demembranated sea urchin sperm flagella. *J Cell Biol.* 1979;82:401-411.
60. Ho HC, Granish KA, Suarez SS. Hyperactivated motility of bull sperm is triggered at the axoneme by Ca^{2+} and not cAMP. *Dev Biol.* 2002;250:208-217.
61. Olson SD, Suarez SS, Fauci LJ. A model of CatSper channel mediated calcium dynamics in mammalian spermatozoa. *Bull Math Biol.* 2010;72:1925-1946.
62. Olson SD, Fauci LJ, Suarez SS. Mathematical modeling of calcium signaling during sperm hyperactivation. *Mol Hum Reprod.* 2011;17:500-510.
63. Lishko PV, Kirichok Y, Ren D, Navarro B, Chung JJ, Clapham DE. The control of male fertility by spermatozoan ion channels. *Annu Rev Physiol.* 2012;74:453-475.
64. Qi H, Moran MM, Navarro B et al. All four CatSper ion channel proteins are required for male fertility and sperm cell hyperactivated motility. *Proc Natl Acad Sci USA.* 2007;104:1219-1223.
65. Smith JF, Syritsyna O, Fellous M et al. Disruption of the principal, progesterone-activated sperm Ca^{2+} channel in a CatSper2-deficient infertile patient. *Proc Natl Acad Sci USA.* 2013;110:6823-6828.
66. Carlson AE, Westenbroek RE, Quill T et al. CatSper1 required for evoked Ca^{2+} entry and control of flagellar function in sperm. *Proc Natl Acad Sci USA.* 2003;100:14864-14868.
67. Quill TA, Sugden SA, Rossi KL, Doolittle LK, Hammer RE, Garbers DL. Hyperactivated sperm motility driven by CatSper2 is required for fertilization. *Proc Natl Acad Sci USA.* 2003;100:14869-14874.
68. Johnson GP, English AM, Cronin S, Hoey DA, Meade KG, Fair S. Genomic identification, expression profiling, and functional characterization of CatSper channels in the bovine. *Biol Reprod.* 2017;97:302-312.
69. Vicente-Carrillo A, Álvarez-Rodríguez M, Rodríguez-Martínez H. The CatSper channel modulates boar sperm motility during capacitation. *Reprod Biol.* 2017;17:69-78.
70. Marquez B, Ignatz G, Suarez SS. Contributions of extracellular and intracellular Ca^{2+} to regulation of sperm motility: Release of intracellular stores can hyperactivate CatSper1 and CatSper2 null sperm. *Dev Biol.* 2007;303:214-221.
71. Ho HC, Suarez SS. Characterization of the intracellular calcium store at the base of the sperm flagellum that regulates hyperactivated motility. *Biol Reprod.* 2003;68:1590-1596.
72. Harayama H, Murase T, Miyake M. A cyclic adenosine 3',5'-monophosphate stimulates phospholipase Cgamma1-calcium signaling via the activation of tyrosine kinase in boar spermatozoa. *J Androl.* 2005;26:732-740.
73. Harper CV, Barratt CL, Publicover SJ. Stimulation of human spermatozoa with progesterone gradients to simulate approach to the oocyte. Induction of $[\text{Ca}^{2+}]_i$ oscillations and cyclical transitions in flagellar beating. *J Biol Chem.* 2004;279:46315-46325.
74. Yoshida M, Yoshida K. Sperm chemotaxis and regulation of flagellar movement by Ca^{2+} . *Mol Hum Reprod.* 2011;17:457-465.
75. Ignatz GG, Suarez SS. Calcium/calmodulin and calmodulin kinase II stimulate hyperactivation in demembranated bovine sperm. *Biol Reprod.* 2005;73:519-526.
76. Miyata H, Satouh Y, Mashiko D et al. Sperm calcineurin inhibition prevents mouse fertility with implications for male contraceptive. *Science.* 2015;350:442-445.
77. Itach SB, Finklestein M, Etkovitz N, Breitbart H. Hyper-activated motility in sperm capacitation is mediated by phospholipase D-dependent actin polymerization. *Dev Biol.* 2012;362:154-161.
78. Mizuno K, Shiba K, Okai M et al. Calaxin drives sperm chemotaxis by Ca^{2+} -mediated direct modulation of a dynein motor. *Proc Natl Acad Sci USA.* 2012;109:20497-20502.
79. Inaba K. Calcium sensors of ciliary outer arm dynein: functions and phylogenetic considerations for eukaryotic evolution. *Cilia.* 2015;4:6.
80. Shojima T, Hou F, Takahashi Y et al. Crystal structure of a Ca^{2+} -dependent regulator of flagellar motility reveals the open-closed structural transition. *Sci Rep.* 2018;8:2014.
81. Navarrete FA, Alvau A, Lee HC et al. Transient exposure to calcium ionophore enables in vitro fertilization in sterile mouse models. *Sci Rep.* 2016;6:33589.
82. Nishigaki T, José O, González-Cota AL, Romero F, Treviño CL, Darszon A. Intracellular pH in sperm physiology. *Biochem Biophys Res Commun.* 2014;450:1149-1158.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Harayama H. Flagellar hyperactivation of bull and boar spermatozoa. *Reprod Med Biol.* 2018;17:442-448. <https://doi.org/10.1002/rmb2.12227>