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## JOURNAL ARTICLE

# Interaction between $\text{Ca}^{2+}$ , cyclic 3',5' adenosine monophosphate, the superoxide anion, and tyrosine phosphorylation pathways in the regulation of human sperm capacitation

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In order to fertilize the egg, spermatozoa must go through the capacitation process where they experience  $\text{Ca}^{2+}$  uptake, increases in cyclic 3',5' adenosine monophosphate (cAMP) concentrations, superoxide anion production, and protein tyrosine phosphorylation. Although the importance of these processes has been described, the interactions between them, as well as the temporal sequence of these events, remain to be demonstrated. Previous studies from our laboratory have demonstrated that tyrosine phosphorylation of p105 and p81 (p105/81), the two major human sperm phosphotyrosine-containing proteins, was under cAMP and oxygen derivatives regulation. In the present study, we investigated the importance of intra- and extracellular  $\text{Ca}^{2+}$ , as well as the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine and the phosphatase inhibitors calyculin A and okadaic acid, in the production of superoxide anion and p105/81 tyrosine phosphorylation. An increase in p105/81 phosphotyrosine content was observed when spermatozoa were incubated in the absence of extracellular  $\text{Ca}^{2+}$  or with the calmodulin antagonist N-(6-aminohexyl)-1-naphthalenesulfonamide. However, the human sperm capacitation inducer FCSu (ultrafiltrate of fetal cord serum) requires the presence of the extracellular  $\text{Ca}^{2+}$  to induce capacitation, superoxide anion production, and tyrosine phosphorylation of p105/81, whereas free intracellular  $\text{Ca}^{2+}$  had no effect on these last two processes. The production of superoxide anion by spermatozoa was stimulated by inhibitors of phosphodiesterases and serine/threonine phosphoprotein phosphatases. The tyrosine phosphatase inhibitor vanadate decreased by 40% the FCSu-stimulated superoxide anion production, although it had no effect when used alone. These results suggest that, during sperm capacitation,  $\text{Ca}^{2+}$  induces an elevation in cAMP levels; this cAMP, through undefined serine/threonine protein phosphorylation, stimulates the generation of superoxide anion, which, in turn, causes the increase in p105/81 phosphotyrosine contents.

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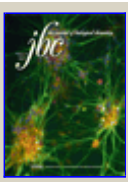
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Expression of Hsp60 and Grp78 in the human endometrium and oviduct, and their effect on sperm functions  
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Ontogeny of Tyrosine Phosphorylation-Signaling Pathways During  
Spermatogenesis and Epididymal Maturation in the Mouse  
Biol Reprod, October 1, 2006; 75(4): 588 - 597.

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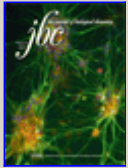


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Na<sup>+</sup>/K<sup>+</sup>ATPase as a Signaling Molecule During Bovine Sperm  
Capacitation  
Biol Reprod, September 1, 2006; 75(3): 308 - 317.

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## JBC Online

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M. T. Branham, L. S. Mayorga, and C. N. Tomes  
Calcium-induced Acrosomal Exocytosis Requires cAMP Acting  
through a Protein Kinase A-independent, Epac-mediated Pathway  
J. Biol. Chem., March 31, 2006; 281(13): 8656 - 8666.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



## Molecular Human Reproduction

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J. Laflamme, A. Akoum, and P. Leclerc  
Induction of human sperm capacitation and protein tyrosine  
phosphorylation by endometrial cells and interleukin-6  
Mol. Hum. Reprod., February 1, 2005; 11(2): 141 - 150.

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W.C.L. Ford  
Regulation of sperm function by reactive oxygen species  
Hum. Reprod. Update, September 1, 2004; 10(5): 387 - 399.

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## Journal of ANDROLOGY

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V. Nauc, E. De Lamirande, P. Leclerc, and C. Gagnon  
Inhibitors of Phosphoinositide 3-Kinase, LY294002 and Wortmannin,  
Affect Sperm Capacitation and Associated Phosphorylation of  
Proteins Differently: Ca<sup>2+</sup>-Dependent Divergences  
J Androl, July 1, 2004; 25(4): 573 - 585.

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## Molecular Human Reproduction

▶ HOME

C. O'Flaherty, E. de Lamirande, and C. Gagnon  
Phosphorylation of the Arginine-X-X- (Serine/Threonine) motif in  
human sperm proteins during capacitation: modulation and protein  
kinase A dependency  
Mol. Hum. Reprod., May 1, 2004; 10(5): 355 - 363.

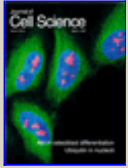
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J. Rivlin, J. Mendel, S. Rubinstein, N. Etkovitz, and H. Breitbart  
Role of Hydrogen Peroxide in Sperm Capacitation and Acrosome  
Reaction

Biol Reprod, February 1, 2004; 70(2): 518 - 522.

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**Journal of Cell Science**[▶ HOME](#)

M. A. Baker, L. Hetherington, H. Ecroyd, S. D. Roman, and R. J. Aitken  
Analysis of the mechanism by which calcium negatively regulates  
the tyrosine phosphorylation cascade associated with sperm  
capacitation

J. Cell Sci., January 15, 2004; 117(2): 211 - 222.

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H. W. Ecroyd, R. C. Jones, and R. J. Aitken  
Endogenous Redox Activity in Mouse Spermatozoa and Its Role in  
Regulating the Tyrosine Phosphorylation Events Associated with  
Sperm Capacitation

Biol Reprod, July 1, 2003; 69(1): 347 - 354.

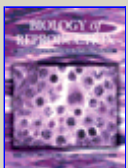
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A. M. Petrunkina, K. Simon, A.-R. Gunzel-Apel, and E. Topfer-Petersen  
Specific Order in the Appearance of Protein Tyrosine Phosphorylation  
Patterns Is Functionally Coordinated With Dog Sperm  
Hyperactivation and Capacitation

J Androl, May 1, 2003; 24(3): 423 - 437.

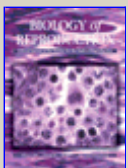
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J. Thundathil, E. de Lamirande, and C. Gagnon  
Nitric Oxide Regulates the Phosphorylation of the Threonine-  
Glutamine-Tyrosine Motif in Proteins of Human Spermatozoa During  
Capacitation

Biol Reprod, April 1, 2003; 68(4): 1291 - 1298.

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A. C. Pommer, J. Rutllant, and S. A. Meyers  
Phosphorylation of Protein Tyrosine Residues in Fresh and  
Cryopreserved Stallion Spermatozoa under Capacitating Conditions

Biol Reprod, April 1, 2003; 68(4): 1208 - 1214.

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**Molecular Human Reproduction**[▶ HOME](#)

V. Dorval, M. Dufour, and P. Leclerc  
Role of protein tyrosine phosphorylation in the thapsigargin-induced  
intracellular Ca<sup>2+</sup> store depletion during human sperm acrosome  
reaction

Mol. Hum. Reprod., March 1, 2003; 9(3): 125 - 131.

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**BIOLOGY of REPRODUCTION**[▶ HOME](#)

V. Dorval, M. Dufour, and P. Leclerc  
Regulation of the Phosphotyrosine Content of Human Sperm  
Proteins by Intracellular Ca<sup>2+</sup>: Role of Ca<sup>2+</sup>-Adenosine  
Triphosphatases  
Biol Reprod, November 1, 2002; 67(5): 1538 - 1545.  
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**Molecular Human Reproduction**[▶ HOME](#)

J. Thundathil, E. de Lamirande, and C. Gagnon  
Different signal transduction pathways are involved during human  
sperm capacitation induced by biological and pharmacological  
agents  
Mol. Hum. Reprod., September 1, 2002; 8(9): 811 - 816.  
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**BIOLOGY of REPRODUCTION**[▶ HOME](#)

P. Leclerc and S. Goupil  
Regulation of the Human Sperm Tyrosine Kinase c-yes. Activation by  
Cyclic Adenosine 3',5'-Monophosphate and Inhibition by Ca<sup>2+</sup>  
Biol Reprod, July 1, 2002; 67(1): 301 - 307.  
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**Molecular Human Reproduction**[▶ HOME](#)

E. de Lamirande and C. Gagnon  
The extracellular signal-regulated kinase (ERK) pathway is involved  
in human sperm function and modulated by the superoxide anion  
Mol. Hum. Reprod., February 1, 2002; 8(2): 124 - 135.  
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Y. Si and P. Olds-Clarke  
Evidence for the Involvement of Calmodulin in Mouse Sperm  
Capacitation  
Biol Reprod, May 1, 2000; 62(5): 1231 - 1239.  
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**The Journal of Immunology**[▶ HOME](#)

E. Rollet-Labelle, C. Gilbert, and P. H. Naccache  
Modulation of Human Neutrophil Responses to CD32 Cross-Linking  
by Serine/Threonine Phosphatase Inhibitors: Cross-Talk Between  
Serine/Threonine and Tyrosine Phosphorylation  
J. Immunol., January 15, 2000; 164(2): 1020 - 1028.  
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**BIOLOGY of REPRODUCTION**[▶ HOME](#)

A. Mandal, S. Naaby-Hansen, M. J. Wolkowicz, K. Klotz, J. Shetty, J. D.  
Retief, S. A. Coonrod, M. Kinter, N. Sherman, F. Cesar, *et al.*  
FSP95, A Testis-Specific 95-Kilodalton Fibrous Sheath Antigen That  
Undergoes Tyrosine Phosphorylation in Capacitated Human  
Spermatozoa  
Biol Reprod, November 1, 1999; 61(5): 1184 - 1197.  
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