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## Follicle-Stimulating Hormone Induces a Gap Junction-Dependent Dynamic Change in [cAMP] and Protein Kinase A in Mammalian Oocytes

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## Abstract

The second messenger cyclic adenosine 5′monophosphate (cAMP) has been implicated in controlling meiotic maturation. To date, there have been no direct measurements of cAMP in living mammalian oocytes. Here, we have used the fluorescently labelled cAMP-dependent protein kinase A (PKA), FICRhR, to monitor cAMP in mouse oocytes. In cumulus-enclosed oocytes, follicle-stimulating hormone (FSH) stimulated an increase in the oocyte [cAMP] that was prevented by using the gap junction inhibitor, carbenoxolone. The FSH-induced increase in oocyte [cAMP] was suppressed in a time-dependent manner by prior exposure to ATP, while epidermal growth factor had no effect on basal or stimulated levels of cAMP. Finally, using confocal microscopy, we show that the regulatory and catalytic subunits of the microinjected PKA are distributed in a punctate manner with a stronger accumulation in the perinuclear region. On an increase in [cAMP], in response to phosphodiesterase inhibition or FSH, the catalytic subunit diffused throughout the cytoplasm and germinal vesicle, while the regulatory subunit remained anchored. These experiments show that increases in cAMP in ovarian somatic cells are communicated via gap junctions to the oocyte, where it can lead to a redistribution of the catalytic subunit of PKA.

## Keywords





cAMP; FICRhR; PKA; ATP; AKAP; oocyte; gap junction; ovary; mouse






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## References

## REFERENCES

- 1 S. Adams, B. Bacsikai, A.T. Harootunian, S. Mahaut, P.J. Sammak, S.S. Taylor, R.Y. Tsien  
**Imaging of cAMP signals and A-kinase translocation in single living cells**  
Adv. Second Messenger Phosphoprotein Res., 28 (1993), pp. 167-170
- 2 S.R. Adams, A.T. Harootunian, Y.J. Buechler, S.S. Taylor, R.Y. Tsien  
**Fluorescence ratio imaging of cyclic AMP in single cells**  
Nature, 349 (1991), pp. 694-697
- 3 E. Anderson, D.E. Alborini




- 3 E. Anderson, D.F. Albertini  
**Gap junctions between the oocyte and companion follicle cells in the mammalian ovary**  
J. Cell Biol., 71 (1976), pp. 680-686
- 4 D.F. Albertini, C.M.H. Combelles, E. Benecchi, M.J. Carabatsos  
**Cellular basis for paracrine regulation of ovarian follicle development**  
Reproduction, 121 (2001), pp. 647-654
- 5 B.J. Bacskai, B. Hochner, S. Mahaut, S.R. Adams, B.K. Kaang, E.R. Kandel, R.Y. Tsien  
**Spatially resolved dynamics of cAMP and protein kinase A subunits in Aplysia sensory neurons**  
Science, 260 (1993), pp. 222-226
- 6 E.A. Bomslaeager, R.M. Schultz  
**Regulation of mouse oocyte maturation: Effect of elevating cumulus cell cAMP on oocyte cAMP levels**  
Biol. Reprod., 33 (1985), pp. 698-704
- 7 P.T. Brower, R.M. Schultz  
**Intercellular communication between granulosa cells and mouse oocytes: Existence and possible nutritional role during oocyte growth**  
Dev. Biol., 90 (1982), pp. 144-153  
[Article](#)  [PDF \(6MB\)](#)
- 8 I.L. Buxton, L.L. Brunton  
**Compartment of cyclic AMP and protein kinase in mammalian cardiomyocytes**  
J. Biol. Chem., 258 (1983), pp. 10233-10239
- 9 M.J. Carabatsos, C. Sellitto, D.A. Goodenough, D.F. Albertini  
**Oocyte-granulosa cell heterologous gap junctions are required for the coordination of nuclear and cytoplasmic meiotic competence**  
Dev. Biol., 226 (2000), pp. 167-179  
[Article](#)  [PDF \(335KB\)](#)
- 10 D.W. Carr, H. Stofko, I.D. Fraser, S.M. Bishop, T.S. Acott, R.G. Brennan, J.D. Scott  
**Interaction of the regulatory subunit (RII) of cAMP-dependent protein kinase with RII-anchoring proteins occurs through an amphipathic helix binding motif**  
J. Biol. Chem., 266 (1991), pp. 14188-14192
- 11 W.K. Cho, S. Stern, J.D. Biggers  
**Inhibitory effect of dibutyryl cAMP on mouse oocyte maturation in vitro**  
J. Exp. Zool., 187 (1974), pp. 383-386
- 12 J.S. Davidson, I.M. Baumgarten  
**Glycyrrhetic acid derivatives: A novel class of inhibitors of gap-junctional intercellular communication. Structure-activity relationships**  
J. Pharmacol. Exp. Ther., 246 (1988), pp. 1104-1107
- 13 J.S. Davidson, I.M. Baumgarten, E.H. Harley  
**Reversible inhibition of intercellular junctional communication by glycyrrhetic acid**  
Biochem. Biophys. Res. Commun., 134 (1986), pp. 29-36  
[Article](#)  [PDF \(448KB\)](#)
- 14 N. Dekel, W.H. Beers  
**Rat oocyte maturation in vitro: Relief of cyclic AMP inhibition by gonadotropins**  
Proc. Natl. Acad. Sci. USA, 75 (1978), pp. 4369-4373
- 15 N. Dekel, W.H. Beers  
**Development of the rat oocyte in vitro: Inhibition and induction of maturation in the presence or absence of the cumulus oophorus**  
Dev. Biol., 75 (1980), pp. 247-254  
[Article](#)  [PDF \(741KB\)](#)
- 16 N. Dekel, I. Sherizly  
**Epidermal growth factor induces maturation of rat follicle-enclosed oocytes**  
Endocrinology, 116 (1985), pp. 406-409

- 17 S.M. Downs  
**Control of the resumption of meiotic maturation in mammalian oocytes**  
J.G. Grudzinskas, J.L. Yovich (Eds.), *Gametes: The Oocyte*, Cambridge Univ. Press, Cambridge (1995), pp. 150-192
- 18 S.M. Downs, S.A. Daniel, J.J. Eppig  
**Induction of maturation in cumulus cell-enclosed mouse oocytes by follicle-stimulating hormone and epidermal growth factor: Evidence for a positive stimulus of somatic cell origin**  
*J. Exp. Zool.*, 245 (1988), pp. 86-96
- 19 S.M. Downs, D. Hunzicker  
**Differential regulation of oocyte maturation and cumulus expansion in the mouse oocyte-cumulus cell complex by site-selective analogs of cyclic adenosine monophosphate**  
*Dev. Biol.*, 172 (1995), pp. 72-85  
[Article](#)  [PDF \(177KB\)](#)
- 20 R.G. Edwards  
**Maturation in vitro of mouse, sheep, cow, pig, rhesus monkey and human ovarian oocytes**  
*Nature*, 208 (1965), pp. 349-351
- 21 J.J. Eppig, S.M. Downs  
**The effect of hypoxanthine on mouse oocyte growth and development in vitro: Maintenance of meiotic arrest and gonadotropin-induced oocyte maturation**  
*Dev. Biol.*, 119 (1987), pp. 313-321  
[Article](#)  [PDF \(1MB\)](#)
- 22 A. Feliciello, M.E. Gottesman, E.V. Avedimento  
**The biological functions of A-kinase anchor proteins**  
*J. Mol. Biol.*, 308 (2001), pp. 99-114  
[Article](#)  [PDF \(448KB\)](#)
- 23 S.H. Francis, J.D. Corbin  
**Structure and function of cyclic nucleotide-dependent protein kinases**  
*Annu. Rev. Physiol.*, 56 (1994), pp. 237-272
- 24 B.P. Fulton, D.G. Whittingham  
**Activation of mammalian oocytes by intracellular injection of calcium**  
*Nature*, 273 (1978), pp. 149-151
- 25 N.B. Gilula, M.L. Epstein, W.H. Beers  
**Cell-to-cell communication and ovulation. A study of the cumulus-oocyte complex**  
*J. Cell Biol.*, 78 (1978), pp. 58-75
- 26 J.M. Goillard, P.V. Vincent, R. Fischmeister  
**Simultaneous measurements of intracellular cAMP and L-type  $\text{Ca}^{2+}$  current in single frog ventricular myocytes**  
*J. Physiol.*, 530 (2001), pp. 79-91
- 27 G.S. Goldberg, A.P. Moreno, J.F. Bechberger, S.S. Hearn, R.R. Shivers, D.J. MacPhee, Y.C. Zhang, C.C. Naus  
**Evidence that disruption of connexon particle arrangements in gap junction plaques is associated with inhibition of gap junctional communication by a glycyrrhetic acid derivative**  
*Exp. Cell Res.*, 222 (1996), pp. 48-53  
[Article](#)  [PDF \(344KB\)](#)
- 28 A.T. Harootunian, S.R. Adams, W. Wen, J.L. Meinkoth, S.S. Taylor, R.Y. Tsien  
**Movement of the free catalytic subunit of cAMP-dependent protein kinase into and out of the nucleus can be explained by diffusion**  
*Mol. Biol. Cell*, 4 (1993), pp. 993-1002
- 29 F.W. Herberg, A. Maleszka, T. Eide, L. Vossebein, K. Tasken  
**Analysis of A-kinase anchoring protein (AKAP) interaction with protein kinase A (PKA) regulatory subunits: PKA isoform specificity in AKAP binding**  
*J. Mol. Biol.*, 298 (2000), pp. 329-339  
[Article](#)  [PDF \(224KB\)](#)

- 30 W.J. Larsen, S.E. Wert, G.D. Brunner  
**A dramatic loss of cumulus cell gap junctions is correlated with germinal vesicle breakdown in rat oocytes**  
Dev. Biol., 113 (1986), pp. 517-521  
Article  PDF (506KB)
- 31 W.J. Larsen, S.E. Wert, G.D. Brunner  
**Differential modulation of rat follicle cell gap junction populations at ovulation**  
Dev. Biol., 122 (1987), pp. 61-71  
Article  PDF (9MB)
- 32 T.S. Lawrence, W.H. Beers, N.B. Gilula  
**Transmission of hormonal stimulation by cell-to-cell communication**  
Nature, 272 (1978), pp. 501-506
- 33 L. Leibfried, N.L. First  
**Follicular control of meiosis in the porcine oocyte**  
Biol. Reprod., 23 (1980), pp. 705-709
- 34 H.R. Lindner, A. Amsterdam, Y. Salomon, A. Tsafiri, A. Nimrod, S.A. Lamprecht, U. Zor, Y. Koch  
**Intraovarian factors in ovulation: Determinants of follicular response to gonadotrophins**  
J. Reprod. Fertil., 51 (1977), pp. 215-235
- 35 S.M. Lohmann, U. Walter  
**Regulation of the cellular and subcellular concentrations and distribution of cyclic nucleotide-dependent protein kinases**  
Adv. Cyclic Nucleotide Protein Phosphorylation Res., 18 (1984), pp. 63-117
- 36 R.M. Moor, J.P. Heslop  
**Cyclic AMP in mammalian follicle cells and oocytes during maturation**  
J. Exp. Zool., 216 (1981), pp. 205-209
- 37 C.D. Nicolson, R.A.J. Challis, M. Shahid  
**Differential modulation of tissue function and therapeutic potential of selective inhibitors of cyclic nucleotide phosphodiesterase isoenzymes**  
Trends Pharmacol. Sci., 12 (1991), pp. 19-24
- 38 M.G. Newlon, M. Roy, D. Morikis, D.W. Carr, R. Westphal, J.D. Scott, P.A. Jennings  
**A novel mechanism of PKA anchoring revealed by solution structures of anchoring complexes**  
EMBO J., 20 (2001), pp. 1651-1662
- 39 T. Pawson, J.D. Scott  
**Signaling through scaffold, anchoring, and adaptor proteins**  
Science, 278 (1997), pp. 2075-2080
- 40 G. Pincus, E.V. Enzmann  
**The comparative behaviour of mammalian eggs in vivo and in vitro**  
J. Exp. Med., 62 (1935), pp. 655-675
- 41 C. Racowsky  
**Effect of forskolin on the spontaneous maturation and cyclic AMP content of rat oocyte–cumulus complexes**  
J. Reprod. Fertil., 72 (1984), pp. 107-116
- 42 C. Racowsky  
**Effect of forskolin on the spontaneous maturation and cyclic AMP content of hamster oocyte–cumulus complexes**  
J. Exp. Zool., 234 (1985), pp. 87-96
- 43 C. Racowsky, K.V. Baldwin  
**In vitro and in vivo studies reveal that hamster oocyte meiotic arrest is maintained only transiently by follicular fluid, but persistently by membrana/cumulus granulosa cell contact**  
Dev. Biol., 134 (1989), pp. 297-306  
Article  PDF (5MB)
- 44 C.S. Rubin

**A kinase anchor proteins and the intracellular targeting of signals carried by cyclic AMP**

Biochim. Biophys. Acta, 1224 (1994), pp. 467-479

- 45 M.L. Ruehr, D.R. Zakhary, D.S. Damron, M. Bond  
**Cyclic AMP-dependent protein kinase binding to A-kinase anchoring proteins in living cells by fluorescence resonance energy transfer of green fluorescent protein fusion proteins**  
J. Biol. Chem., 274 (1999), pp. 33092-33096
- 46 A. Salustri, S. Petrungaro, F. De, M. Conti, G. Siracusa  
**Effect of follicle-stimulating hormone on cyclic adenosine monophosphate level and on meiotic maturation in mouse cumulus cell-enclosed oocytes cultured in vitro**  
Biol. Reprod., 33 (1985), pp. 797-802
- 47 A. Salustri, G. Siracusa  
**Metabolic coupling, cumulus expansion and meiotic resumption in mouse cumuli oophori cultured in vitro in the presence of FSH or dcAMP, or stimulated in vivo by hCG**  
J. Reprod. Fertil., 68 (1983), pp. 335-341
- 48 R.M. Schultz, R.R. Montgomery, J.R. Belanoff  
**Regulation of mouse oocyte meiotic maturation: Implication of a decrease in oocyte cAMP and protein dephosphorylation in commitment to resume meiosis**  
Dev. Biol., 97 (1983), pp. 264-273  
[Article](#)  [PDF \(1MB\)](#)
- 49 R.M. Schultz, R.R. Montgomery, B. Ward, J.J. Eppig  
**Regulation of oocyte maturation in the mouse: Possible roles of intercellular communication, cAMP, and testosterone**  
Dev. Biol., 95 (1983), pp. 294-304  
[Article](#)  [PDF \(2MB\)](#)
- 50 R.M. Schultz, R.R. Montgomery, B. Ward, J.J. Eppig  
**Regulation of oocyte maturation in the mouse: Possible roles of intercellular communication, cAMP, and testosterone**  
Dev. Biol., 95 (1983), pp. 294-304  
[Article](#)  [PDF \(2MB\)](#)
- 51 J. Smits, R.G. Cortvriendt  
**The earliest stages of folliculogenesis in vitro**  
Reproduction, 123 (2002), pp. 185-202
- 52 S.W. Spaulding  
**The ways in which hormones change cyclic adenosine 3',5'-monophosphate-dependent protein kinase subunits, and how such changes affect cell behavior**  
Endocr. Rev., 14 (1993), pp. 632-650
- 53 S.A. Stricker, T.L. Smythe  
**5-HT causes an increase in cAMP that stimulates, rather than inhibits, oocyte maturation in marine nemertean worms**  
Development, 128 (2001), pp. 1415-1427
- 54 C.J. Tai, S.K. Kang, P.C. Leung  
**Adenosine triphosphate-evoked cytosolic calcium oscillations in human granulosa-luteal cells: Role of protein kinase C**  
J. Clin. Endocrinol. Metab., 86 (2001), pp. 773-777
- 55 A. Tsafiri, C.P. Channing  
**An inhibitory influence of granulosa cells and follicular fluid upon porcine oocyte meiosis in vitro**  
Endocrinology, 96 (1975), pp. 922-927
- 56 A. Tsafiri, H.R. Lindner, U. Zor, S.A. Lamprecht  
**In-vitro induction of meiotic division in follicle-enclosed rat oocytes by LH, cyclic AMP and prostaglandin E 2**  
J. Reprod. Fertil., 31 (1972), pp. 39-50
- 57 A. Tsafiri, S.Y. Chun, R. Zhang, A.J. Hsueh, M. Conti  
**Oocyte maturation involves compartmentalization and opposing changes of cAMP levels in follicular somatic and germ cells: Studies using selective phosphodiesterase inhibitors**  
Dev. Biol., 178 (1996), pp. 393-402

- 58 E. Vivarelli, M. Conti, F. De, G. Siracusa  
**Meiotic resumption and intracellular cAMP levels in mouse oocytes treated with compounds which act on cAMP metabolism**  
Cell Differ., 12 (1983), pp. 271-276  
Article  PDF (414KB)
- 59 C. Vozzi, A. Formenton, A. Chanson, A. Senn, R. Sahli, P. Shaw, P. Nicod, M. Germond, J.-A. Haefliger  
**Involvement of connexin 43 in meiotic maturation of bovine oocytes**  
Reproduction, 122 (2001), pp. 619-628
- 60 R.J. Webb, H. Bains, C. Cruttwell, J. Carroll  
**Gap-junctional communication in mouse cumulus oocyte complexes: Implications for the mechanism of meiotic maturation**  
Reproduction, 123 (2002), pp. 41-52
- 61 C.S. Wright, D.L. Becker, J.S. Lin, A.E. Warner, K. Hardy  
**Stage-specific and differential expression of gap junctions in the mouse ovary: Connexin-specific roles in follicular regulation**  
Reproduction, 121 (2001), pp. 77-88
- 62 Y. Yoshimura, Y. Nakamura, M. Ando, M. Jinno, T. Oda, M. Karube, N. Koyama, T. Nanno  
**Stimulatory role of cyclic adenosine monophosphate as a mediator of meiotic resumption in rabbit oocytes**  
Endocrinology, 131 (1992), pp. 351-356
- 63 Y. Yoshimura, Y. Nakamura, T. Oda, M. Ando, Y. Ubukata, M. Karube, N. Koyama, H. Yamada  
**Induction of meiotic maturation of follicle-enclosed oocytes of rabbits by a transient increase followed by an abrupt decrease in cyclic AMP concentration**  
J. Reprod. Fertil., 95 (1992), pp. 803-812
- 64 M. Zaccolo, G. De, C.Y. Cho, L. Feng, T. Knapp, P.A. Negulescu, S.S. Taylor, R.Y. Tsien, T. Pozzan  
**A genetically encoded, fluorescent indicator for cyclic AMP in living cells**  
Nat. Cell Biol., 2 (2000), pp. 25-29

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