Synergistic activities of multiple cyclic AMP phosphodiesterases prevent premature meiotic progression, ovulation, and progesterone signaling in mouse ovarian follicles

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Introduction
In the mammalian ovary, most of the cellular responses to LH are mediated by elevation of cyclic AMP in the somatic cells surrounding the oocyte. To avoid premature responses, cAMP concentration must be finely regulated and regulation occurs on multiple levels, including the activity of cAMP phosphodiesterases (PDEs) (1, 2). Among the cAMP PDEs expressed by preovulatory granulosa cells in rat, mouse and human, PDE7 and PDE8 show the highest mRNA levels, with lower expression of PDE4 (3, 5). This raises the question of whether these three PDEs act synergistically, as seen in other systems (6). To address this question, we tested the effects of inhibiting these PDEs, alone or in combination, using specific inhibitors, on meiotic resumption, ovulation and progesterone signaling in mouse ovarian follicles.

mRNA expression of PDEs in mouse preovulatory follicles and selectivity of the cAMP PDEs inhibitors. A. Preovulatory granulosa cells constitutively express at least 10 different PDEs, most of which have cAMP-hydrolyzing activity. Among these, PDE8 and PDE7 show the highest mRNA expression, with a much lower expression of PDE4. B. The inhibitors used in this study showed high selectivity in inhibiting single PDEs, with minor effects on the activity of the other PDEs studied.

Results
PDE4, PDE7 and PDE8 act synergistically to suppress spontaneous meiotic resumption in follicle-enclosed oocytes.

A. A mouse follicle-enclosed oocyte after 24 hours of culture on a Millicell membrane, before treatment with LH or cAMP PDE inhibitors. B. Percent of follicles either with LH or PDE4 and PDE7 inhibitors. C. 24 hour time course of NEBD after treatment of follicles with LH, individual inhibitors or a mixture of all three. * Data shown as mean ± s.e.m. for the indicated number of experiments. Different letters indicate statistically significant differences (p=0.05).

Conclusions
Our findings indicate that the CAMP phosphodiesterases PDE4, PDE7 and PDE8 act together in the granulosa cells of the mouse ovarian follicle to suppress CAMP fluctuations that could cause premature meiotic progression, progesterone production, PGR expression and ovulation prior to the LH surge. Precise control of the timing of CAMP elevation in the granulosa cells ensures that the release of the egg is coordinated with other events leading to fertilization.


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