CHANGES IN OVARIAN CONTRACTION BY ENDOTHELIN-2/RECEPTOR SYSTEM IN THE FELINE OVARY

Joseph Cacioppo[1], Patrick Lin[1], Sangwook Oh[1,2], Arnon Gal[1], Yongbum Koo[1,3], CheMyong Ko[1]

[1]Comparative Biosciences, College of Veterinary Medicine, University of Illinois, Urbana-Champaign, Illinois, U.S.;
[2]Biology Education, Chunbuk National University, Jeonju, South Korea;
[3]Department of Biotechnology and Biomedical Science, Inje University, Gimhae, South Korea

Endothelin-2 (ET-2) is transiently expressed in the granulosa cells of mammalian periovulatory follicles immediately prior to ovulation. *Ex vivo* experiments showed that, upon treatment with ET-2, the rodent ovary rapidly contracts. When the endothelin receptor pathway is antagonized *in vivo*, ovulation is inhibited in rodents. These findings led us to postulate that ET-2–induced contraction of smooth muscles in the ovarian cortex is a final trigger for follicle rupture at the time of ovulation. Similar to humans and other mammals, feline ovaries possess a layer of contractile smooth muscle-like cells around developing follicles, known as the theca externa. In addition, feline ovaries have been documented to spontaneously contract *ex vivo*; however, the function of this spontaneous contraction and whether ET-2 induces ovulation remains to be determined. Here, we investigated the characteristics of feline ovarian cortical contraction using myography in the absence or presence of physiological doses of ET-2. Whole fresh feline ovaries were collected after spay procedures through the Junior Surgery Program of the College of Veterinary Medicine at the University of Illinois. Of 13 ovaries tested, all demonstrated a period of strong and sustained contraction when washed with a 50 nM solution of feline ET-2 peptide for 30 minutes, with an average increase in base tensile force of 2.48 ± 0.40 mN. Additionally, when washed for 20 minutes with a 140 nM solution of the dual ET receptor antagonist tezosentan contraction was reduced in a dose-dependent manner. Of these ovaries, 4 demonstrated spontaneous contractions prior to ET-2 treatment, with average amplitude of 4.08 ± 2.45 mN, duration of 22.2 ± 6.4sec, and a time of 60.9 ± 20.2sec between contractions. These contractions continued after ET-2 treatment, but contraction amplitude was reduced (1.25 ± 0.95 mN) as was the time between contractions (13.8 ± 6.5 sec) for all ovaries. There was no change in the duration of these contractions (20.13 ± 4.66 sec). Measurement of mRNA expression by polymerase chain reaction showed that feline ovaries express mRNA for ET-2, both isotypes of endothelin receptors (ET-A and ET-B), and endothelin converting enzymes 1 and 2 (ECE-1 and ECE-2). This study demonstrates that ET-2 produces a feline ovarian cortical contraction. Future work will determine the impact of inhibiting ET-2 and the endothelin receptor pathways *in vivo* on follicle rupture in the feline ovary.

This work was supported by NIH (R01HD052694 to CK).