Opposing roles of endothelin receptors in regulating ovulation and luteal function

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Endothelin receptors, ETA and ETB, often elicit opposing physiologicaly events upon activation by an endothelin. Previously, we showed that both forms of endothelin receptors are present in the ovary, ETA being predominantly localized in the smooth muscle cells of theca externa and blood vessels whease ETB in the endocrine cells of theca interna. We also showed that endothelin-2 is the dominant endothelin isoform and is transiently produced by the ovulatiing follicle prior to ovulation to occur. In the current study, we aimed to determine how a concomitant activation of ETA and ETB would aid three key ovarian events – ovulation, luteal formation and luteal regression. To this end, experimental approaches that antagonized ETA, ETB or both receptor mediated pathways were applied via pharmacological and genetic modulations, and their physiolgical outcomes assessed. These approaches resulted in the following outcomes:

1. Upon treatment with endothelin-2, ETA induced constriction in the ovary while ETB elicited relaxation.
2. Selective null mutation of ETA in the smooth muscle cells of adult mice resulted in the loss of contractile response to endothelin-2 in the ovary and ovulalatory failure.
3. Rescued ETB knockout (rETBKO) mice were hyper-fertile: rETBKO mice produced larger litter sizes than wild type (WT) (7.9±0.7 pups/mouse in rETBKO vs. 5.5±0.1 in WT, $p<0.001$, n=12), had bigger copra lutea (CL) (389.5±12.2 μm^3/ovary in rETBKO vs. 310.1±18.2, $p<0.01$, n=10) and more CL (17.8±2.3 CL/ovary in rETBKO vs. 8.8±0.5 in WT, $p<0.02$, n=10). The rETBKO mice express ETB in adrenergic lineage organs but not in other organs including ovary.
4. EDN2 knockout mice did not ovulate. Nor, they form CL.
5. Systemic injection of tezosentan, a dual endothelin receptor antagonist, immediately after ovulation inhibited angiogenesis and CL formation whereas injection after CL formation delayed CL regression.

Collectively, the results indicate that endothelins promote ovulation and CL formation via ETA-mediated pathways by inducing ovarian constriction and angiogenesis. The same endothelins may negate biological outcomes of ETA-induced pathways via ETB receptor pathways by eliciting muscular relaxation and antagonizing angiogenesis. Therefore, having both ETA and ETB expressed in the ovary may allow a temporal control of critical events involved in the ovulation and luteal function: ETA as an initiator vs. ETB as a terminator. It will be interesting to see whether ETA and ETB exert maximal physiological effects at different concentrations of endothelins in the ovary.