Investigating the Ovary Specificity of Proprotein Convertases to Evaluate for their Non-hormonal Contraceptive Candidacy

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Traditional hormone-based female contraceptives can cause undesired side effects including depression, stroke, obesity, and hormone-related cancers for susceptible populations. *Pcsk3, Pcsk5A, Pcsk5B*, and *Pcsk6*, members of the proprotein convertase (PC) family, have recently emerged as potential targets for developing nonhormonal contraceptives. Our RNA-sequencing analysis revealed that they are continuously upregulated in ovulating follicles. Inhibitors of PCs were found to dose-dependently inhibit ovulation without affecting secretion of estradiol, testosterone, and progesterone. However, the high abundance of PC expression across tissues poses questions about potential toxicity of their inhibitors. The purpose of this experiment was to establish the expression profiles of the 4 mentioned PC isoforms in various mouse tissues to determine their tissue specificity. Mouse tissue samples were collected including oviduct, uterus, liver, kidney, heart, lung, adrenal, spleen, brain, skeletal muscle, and intestine. Ovary and antral follicle samples, stimulated to ovulate with Human chorionic gonadotropin (hCG), were also collected at 0-, 4-, and 8-hours post-stimulation for total RNA extraction and reverse transcription quantitative polymerase chain reaction (RT-qPCR). The results of RT-qPCR showed that *Pcsk5A* expression was highly abundant in the antral follicle and ovary at 8-hours post stimulation, while there was also comparably high expression of *Pcsk5A* in the adrenal gland. With a necessity to determine adrenal related toxicity in future in vivo studies, *Pcsk5A* presents as a promising target for hormone-independent contraception due to its ovary specificity. Supported by the NIH R25ES020721 Grant, the Bill and Melinda Gates Foundation, and the American Society for Pharmacology and Experimental Therapeutics SURF Program.