

Expression of melanocortin receptors in human endometrium

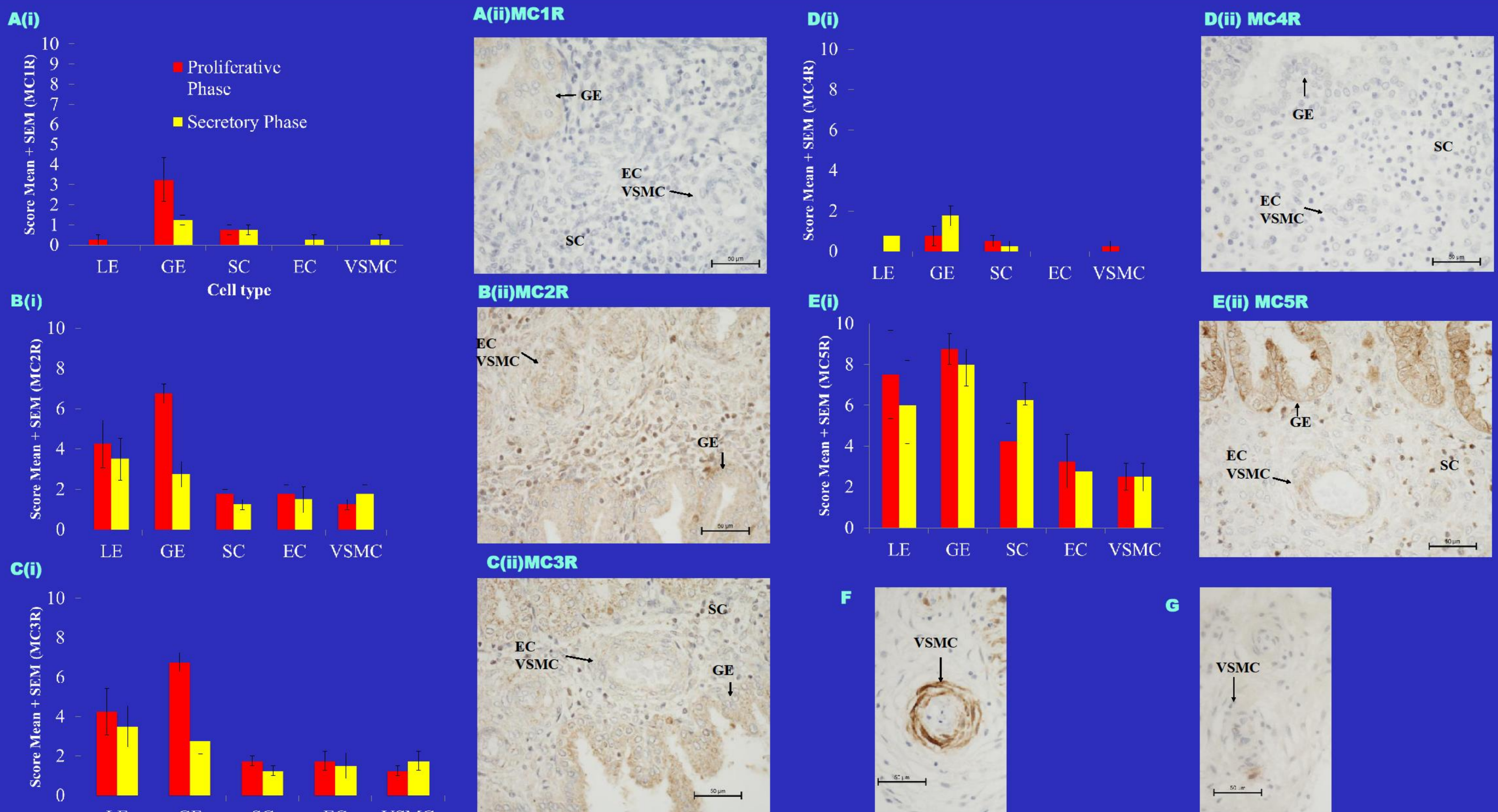
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Background

- The melanocortin system is known to be involved in the hypothalamic regulation of energy balance, which is implicated in reproduction.
- A peripheral role for MCR signalling in the reproductive system has not been described.
- During a clinical trial (RoSA study) of repeated high dose tetracosactide (ACTH₁₋₂₄) injection, four of 9 premenopausal women with Addison's disease developed menstrual disturbances.
- Were these adverse effects mediated via melanocortin signalling in human endometrium?

Method

- 8 endometrial biopsies were obtained from pre-menopausal women after hysterectomy for non endometrial pathology.
- Decidual (8-10 weeks gestation; n=7) tissues were obtained after termination of apparently normal pregnancies.
- The localisation of the expression of melanocortin receptors (MCR 1-5) in the human endometrium was performed using immunocytochemistry.
- Tissue culture was used to characterize the effects of ACTH₁₋₂₄ on decidual tissue.
- The blood vessel integrity was studied using immunostaining of endothelial cells with vascular smooth muscle cell (VSMC) markers.



Figures A-E: Schematic representation of modified quickscore (mean \pm SEM) (i) and representative photomicrograph (ii) (original magnification 400x) of endometrial biopsies immunostained for A) MC1R; B) MC2R; C) MC3R; D) MC4R; E) MC5R. LE – luminal epithelium, GE – glandular epithelium, SC – stromal cells, EC – endothelial cells, VSMC – vascular smooth muscle cells. N=4 each group.

Figure F & G represent photomicrographs of decidual biopsies cultured in synthetic ACTH for 3 days and immunostained for H-Caldesmon to identify vascular smooth muscle cells. F) control sample, G) after culture in 500ng/ml synthetic ACTH. N=7 each group.

Discussion

- The robust expression of MC5R in the luminal and glandular epithelia of human endometrium is consistent with a role for MC5R in secretory epithelia. Their expression on the endometrial vasculature also suggests that ACTH may have a direct effect on vascular development or remodelling.
- MC3R is predominantly expressed in the central nervous system to coordinate feeding rhythms, energy expenditure and homeostasis. Moderate to strong MC3R expression was demonstrated in endometrial epithelial structures and might be associated to the altered energy intake and food preferences reported in women during different phases of the menstrual cycle.
- Robust expression of MC2R in glandular epithelium and to a lesser degree in stromal cells of human endometrium, suggesting a role for ACTH in regulating endometrial glandular secretions.

Conclusion

- This is the first study to demonstrate widespread expression of melanocortin receptors within the endometrium.
- High concentrations of ACTH₁₋₂₄ appeared to promote involution of vascular structures in cultured decidual tissue. This could form the basis of the observed side-effects seen in the participants of our trial of ACTH therapy.
- It is intriguing to consider whether there may be a melanocortin/ACTH system that centrally regulates feeding behaviour in coordination with the menstrual cycle.

