【Grant-in-Aid for Scientific Research (S)】

Broad Section F

Title of Project：Exploration of estrogen feedback mechanisms regulating animal reproduction to improve the methods controlling ovulation and follicle development in domestic animals

TSUKAMURA Hiroko

(Nagoya University, Graduate School of Bioagricultural Sciences, Professor)

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Keyword： folliculogenesis, ovulation, kisspeptin neurons, reproductive technology for livestock

【Purpose and Background of the Research】

It is well known that folliculogenesis and ovulation are controlled by estrogen feedback actions on gonadotropin-releasing hormone (GnRH)/gonadotropin secretion in female mammals. Estrogen produced by ovarian follicles fine-tunes pulsatile GnRH secretion to keep circulating levels of gonadotropins adequately via estrogen negative feedback action. Estrogen production and release gradually increase along with the follicular development, and consequent high levels of circulating estrogen derived from mature follicles, in turn, induce GnRH/luteinizing hormone (LH) surge and ovulation via estrogen positive feedback action. To date, it is well accepted that estrogen receptor α (ERα)-expressing kisspeptin neurons mainly mediate the estrogen feedback on GnRH secretion in mammals, but the molecular mechanisms mediating the estrogen feedback actions remain to be fully elucidated. Many reproductive disorders in livestock and humans are thought to be caused by abnormalities in the estrogen feedback mechanisms, and innovation of reproductive technology based on the mechanisms mediating the estrogen feedback is warranted.

This study aims to elucidate the molecular mechanisms mediating the estrogen feedback actions on GnRH secretion for an improvement of reproductive technology to control folliculogenesis and ovulation in livestock such as cows and goats.

【Research Methods】

I. Elucidation of the molecular mechanism mediating positive and negative feedback actions of estrogen using the rat as a model animal: We investigate candidate factors, such as transcription factors and receptors that control the gene expression and release of kisspeptin in hypothalamic kisspeptin neurons, which mediate estrogen feedback actions on GnRH/gonadotropin secretion.

II. Evaluation of physiological roles of candidates by generating kisspeptin neuron-specific gene-modified rats: We plan to determine the physiological roles of the candidates in the mechanism regulating kisspeptin gene expression and release by generating knockout rats lacking the candidate gene in kisspeptin neurons or the candidate factor gene-specific reporter rats.

III. Identification and functional analysis of afferent neurons that directly regulate kisspeptin neurons: We plan to visualize and identify the afferent neurons that directly regulate kisspeptin neurons by using neuronal tracers. In addition, we will screen compound libraries to identify compounds that act on candidate receptors expressed on kisspeptin neurons.

IV. Verification and applied research in domestic animals: We plan to verify the effects of the candidates on reproductive function in cows and goats (as a model of ruminants). Furthermore, we plan to examine the therapeutic effects of the candidates on reproductive performance in cows showing reproductive disorders, and identify effective compounds for the treatment.

【Expected Research Achievements and Scientific Significance】

The expected results are the identification of factors and receptors that mediate the positive and negative feedback actions of estrogen on the expression and secretion of kisspeptin, which controls reproductive functions, and the acquisition of knowledge that contributes to establishing new reproductive technologies that improve reproductive performance in livestock.

The technology based on the knowledge obtained from this research is of great significance to contribute to improving technological innovation in the field of livestock production and human reproductive medicine.

【Publications Relevant to the Project】

- Tsukamura H. (2021) Kobayashi Award 2019: The neuroendocrine regulation of the mammalian reproduction. Gen Comp Endocrinol, https://doi.org/10.1016/j.ygcen.2021.113755.
- Nagae M, Uenoyama Y, Okamoto S, Tsuchida H, Ikegami K, Goto T, Majarune S, Nakamura S, Sanbo M, Hirabayashi M, Kobayashi K, Inoue N, Tsukamura H. (2021) Direct evidence that KNDy neurons maintain gonadotropin pulses and folliculogenesis as the GnRH pulse generator. Proc Natl Acad Sci USA, 118: e2009156118.
- Tsuchida H, Kawai N, Yamada K, Takizawa M, Inoue N, Uenoyama Y, Tsukamura H. (2021) Central μ-opioid receptor antagonism blocks glucoprivic LH pulse suppression and gluconeogenesis/feeding in female rats. Endocrinology, bqab140 (in press).
- Tsuchida H, Mostari P, Yamada K, Miyazaki S, Enomoto Y, Inoue N, Uenoyama Y, Tsukamura H. (2020) Paraventricular dynorphin A neurons mediate LH pulse suppression induced by hindbrain glucoprivation in female rats. Endocrinology, 161: bqaa161.

【Homepage Address and Other Contact Information】

Laboratory of Animal Reproduction, Graduate School of Bioagricultural Sciences, Nagoya University.
http://www.agr.nagoya-u.ac.jp/~hanshoku/ReprodWeb/