

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



**Title of Project : Demonstration of Novel Brain Molecular
Mechanisms Regulating Reproduction**

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Research Area : Comparative Endocrinology, Neuroendocrinology, Reproductive Biology

Keyword : Hypothalamic hormone, Pituitary hormone, Reproduction

【Purpose and Background of the Research】

Background: The long history of "*neuroendocrine science*" teaches us that the identification of "*novel neuropeptides*" regulating the reproductive axis is essential for the progress of this research field. Reproductive function of vertebrates depends on the stimulatory action of gonadotropin-releasing hormone (GnRH), secreted by the hypothalamus. Until 2000, a hypothalamic neuropeptide inhibiting gonadotropin secretion was unknown in vertebrates. At this time, Tsutsui and colleagues discovered a novel avian hypothalamic neuropeptide that inhibits gonadotropin release, named gonadotropin-inhibitory hormone (GnIH). GnIH acts on gonadotropes in the pituitary and on GnRH neurons in the hypothalamus via GPR147, a novel G protein-coupled receptor for GnIH, to inhibit gonadal development and maintenance by decreasing gonadotropin release and synthesis in birds. Subsequently we found GnIH in the hypothalamus of a variety of vertebrates from fish to humans. Thus, GnIH is considered to have an evolutionarily conserved role in controlling reproduction across vertebrate species.

Purpose: A gonadotropin inhibitory system is an intriguing concept and provides us with an unprecedented opportunity to study the regulation of reproduction from an entirely novel standpoint. In this project, we will identify GnIH in the brain of protochordates and invertebrates as well. We will demonstrate novel brain molecular mechanisms regulating reproduction by GnIH actions. In this project, we will further analyze the mode of action and functional significance of GnIH underlying the regulation of reproduction. Finally, we will obtain novel therapeutic opportunities for reproductive dysfunction.

【Research Methods】

This project will conduct the following researches.

- (1) GnIH signaling cascade in the target cells, gonadotropes ($\alpha T3$) and GnRH neurons (GT1-7).
- (2) Molecular mechanisms inducing GnIH expression by melatonin and DIO2, a new key gene regulating reproduction, and stress.

(3) Molecular mechanisms regulating reproductive behavior by GnIH.

(4) Effects of GnIH gene silencing by RNA interference (RNAi) in the brain on reproduction and reproductive behavior.

(5) Roles of GnIH and its receptor in human reproductive dysfunction.

(6) Identification of GnIH in the brain of protochordates and invertebrates to characterize evolutionary origin and history of GnIH.

【Expected Research Achievements and Scientific Significance】

This project will demonstrate novel brain molecular mechanisms of the regulation of reproduction by GnIH. The generality of these novel mechanisms across animal species including humans will be obtained. This project will also demonstrate the presence of GnIH in the brain of protochordates and invertebrates and the evolutionary origin of GnIH based on its structural analyses. This project will be beneficial for the development of new therapeutic drugs against reproductive disorders in humans.

【Publications Relevant to the Project】

- Tsutsui et al. (2000) *BBRC* 275, 661-667
Yoshimura et al. (2003) *Nature* 426, 178-181
Ukena & Tsutsui (2005) *Mass Spectrom Rev* 24, 469-486 (review)
Ubuka et al. (2005) *Proc Natl Acad Sci USA* 102, 3052-3057 *Nat Reviews Highlight*
Kriegsfeld et al. (2006) *Proc Natl Acad Sci USA* 103, 2410-2415
Ubuka et al. (2008) *Endocrinology* 149, 268-278.
Nakao et al. (2008) *Nature* 452, 317-322
Kagami et al. (2008) *Nat Genetics* 40, 237-242
Sekita et al. (2008) *Nat Genetics* 40, 243-248
Ubuka et al. (2009) *PLoS ONE* 4, e8400
Tsutsui (2009) *Prog Neurobiol* 88, 76-88 (review)
Doi et al. (2010) *Nat Medicine* 16, 67-74
Tsutsui et al. (2010) *Front Neuroendocrinol* (review), in press

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【Homepage Address and Other Contact Information】

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