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Opinion

How to Contribute to the Progress of Reproductive Neuroendocrinology: Discovery of Novel Neuropeptides Regulating Reproductive Physiology and Behavior

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It is essential to discover novel neuropeptides that regulate the pituitary and brain functions for the progress of reproductive neuroendocrinology. At the beginning of the 1970s, gonadotropin-releasing hormone (GnRH), a hypothalamic neuropeptide stimulating gonadotropin release was discovered by Schally's and Guillemin's groups [1,2]. Subsequently, it has been demonstrated that GnRH is highly conserved among vertebrates [3-5]. Since the discovery of GnRH, it has been believed that GnRH is the sole hypothalamic neuropeptide that regulates gonadotropin release in vertebrates based on extensive studies of GnRH over the next three decades.

However, at the beginning of 2000s, two new key hypothalamic neuropeptides have been found to play key roles in the control of reproductive functions in the last 17 years: gonadotropin-inhibitory hormone (GnIH) and kisspeptin. In 2000, Tsutsui's group discovered GnIH in the quail hypothalamus [6]. GnIH inhibits gonadotropin synthesis and release in birds through an action on GnRH neurons and gonadotropes, mediated via GPR147, a member of the G-protein coupled receptor superfamily [7,8]. Subsequently, GnIHs were identified in other vertebrate species from fish to humans [9-13]. As in birds, mammalian and fish GnIHs inhibit gonadotropin release, indicating that a down-regulation of GnIH in the control of hypothalamo-pituitary-gonadal (HPG) axis has been conserved during evolution [14-19].

In addition, recent studies by Tsutsui's group have demonstrated that GnIH has important functions beyond the control of reproduction [20,21]. Based on these findings, it now appears that GnIH acts on the pituitary and the brain to affect a number of behaviors, including reproductive behavior through changes in neurosteroid, such as neuroestrogen, biosynthesis in the brain [21]. Thus, the following 17 years of GnIH research in collaboration with world's leading laboratories has permitted a more complete understanding of the neuroendocrine control of reproductive physiology and behavior.

Following the discovery of GnIH, kisspeptin, encoded by the *kiss1* gene [22], was also discovered which plays an important role in the up-regulation of the reproductive system in mammals [23-25]. Three independent groups reported that kisspeptin is the cognate ligand for GPR54 [26-28]. The activity of kisspeptin neurons that signal via GPR54 is required for puberty and fertility. Kisspeptin has a stimulatory effect on GnRH neurons leading to the release of GnRH and an up-regulation of the HPG axis, while GnIH down-regulates the HPG axis at the level of the pituitary and/or the level of GnRH neurons. The distinct opposing roles of these two newly discovered neuropeptides indicate that GnIH and kisspeptin act as key neurohormones controlling reproductive activity for reviews, see [14,16-19]. Up until now, the *kiss1* gene has been identified in mammals, amphibians and fish. A paralogous gene of kisspeptin was also discovered in various vertebrates, but not birds, and named the *kiss2* gene [22,29]. *Kiss1* and *kiss2* peptides possess stimulate gonadotropin secretion in vertebrates.

Thus, we now know that GnRH is not the sole hypothalamic neurohormone controlling reproduction in vertebrates. Future studies will shed light onto previously unknown interactions of GnRH with GnIH and kisspeptin and contributed to the progress of reproductive neuroendocrinology.

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Bibliography

1. Matsuo H., *et al*. "Structure of the porcine LH- and FSH-releasing hormone. I. The proposed amino acid sequence". *Biochemical and Biophysical Research Communications* 43 (1971): 1334-1339.

2. Burgus R., *et al*. "Primary structure of the ovine hypothalamic luteinizing hormone-releasing factor (LRF) (LH-hypothalamus-LRF-gas chromatography-mass spectrometry-decapeptide-Edman degradation)". *Proceedings of the National Academy of Sciences of the United States of America* 69 (1972): 278-282.

3. King JA and Millar RP. "Structure of chicken hypothalamic luteinizing hormone-releasing hormone. I. Structural determination on partially purified material". *Journal of Biological Chemistry* 257 (1982): 10722-10728.

4. Miyamoto K., *et al*. "Isolation and characterization of chicken hypothalamic luteinizing hormone-releasing hormone". *Biochemical and Biophysical Research Communications* 107 (1982): 820-827.

5. Sherwood NM., *et al*. "Primary structure of gonadotropin-releasing hormone in lamprey brain". *Journal of Biological Chemistry* 15 (1986): 4812-4819.

6. Tsutsui K., *et al*. "A novel avian hypothalamic peptide inhibiting gonadotropin release". *Biochemical and Biophysical Research Communications* 275 (2000): 661-667.

7. Ubuka T., *et al*. "Melatonin induces the expression of gonadotropin-inhibitory hormone in the avian brain". *Proceedings of the National Academy of Sciences of the United States of America* 102 (2005): 3052-3057.

8. Ubuka T., *et al*. "Gonadotropin-inhibitory hormone inhibits gonadal development and maintenance by decreasing gonadotropin synthesis and release in male quail". *Endocrinology* 147 (2006): 1187-1194.

9. Kriegsfeld LJ., *et al*. "Identification and characterization of a gonadotropin-inhibitory system in the brains of mammals". *Proceedings of the National Academy of Sciences of the United States of America* 103 (2006): 2410-2415.

10. Sawada K., *et al*. "Novel fish hypothalamic neuropeptide". European Journal of Biochemical 269 (2002): 6000-6008.

11. Ubuka T., *et al*. "Gonadotropin-inhibitory hormone identification, cDNA cloning, and distribution in rhesus macaque brain". *The Journal of Comparative Neurology* 517 (2009a): 841-855.

12. Ubuka T., *et al*. "Identification of human GnIH homologs, RFRP-1 and RFRP-3, and the cognate receptor, GPR147 in the human hypothalamic pituitary axis". *PLoS One* 4 (2009b): e8400.

13. Ubuka T., *et al*. "Identification, expression, and physiological functions of Siberian hamster gonadotropin-inhibitory hormone". *Endocrinology* 153 (2012): 373-385.

14. Tsutsui K. "Review: A new key neurohormone controlling reproduction, gonadotropin-inhibitory hormone (GnIH): Biosynthesis, mode of action and functional significance". *Progress of Neurobiology* 88 (2009): 76-88.

15. Tsutsui, K. "Review: How to contribute to the progress of neuroendocrinology: New insights from discovering novel neuropeptides and neurosteroids regulating pituitary and brain functions". *General and Comparative Endocrinology* 227 (2016): 3-15.

16. Tsutsui K and Ubuka T. "Review: GnIH control of feeding and reproductive behaviours". *Front Endocrinology* 7 (2016): 170.

17. Tsutsui K and Ukena K. "Review: Hypothalamic LPXRF-amide peptides in vertebrates: identification, localization and hypophysiotropic activity". *Peptides* 27 (2006): 1121-1129.

18. Tsutsui K., *et al*. "Review: Gonadotropin-inhibitory hormone (GnIH) and its control of central and peripheral reproductive function". *Front Neuroendocrinology* 31 (2010a): 284-295.

19. Tsutsui K., *et al*. "Review: Discovery and evolutionary history of gonadotrophin-inhibitory hormone and kisspeptin: new key neuropeptides controlling reproduction". *Journal of Neuroendocrinology* 22 (2010b): 716-727.

20. Tobari Y., *et al*. "A new pathway mediating social effects on the endocrine system: female presence acting via norepinephrine release stimulates gonadotropin-inhibitory hormone in the paraventricular nucleus and suppresses luteinizing hormone in quail". *Journal of Neuroscience* 34 (2014): 9803-9811.

21. Ubuka T., *et al*. "Hypothalamic inhibition of socio-sexual behaviours by increasing neuroestrogen synthesis". *Nature Communications* 5 (2014): 3061.

22. Lee YR., *et al*. "Molecular evolution of multiple forms of kisspeptins and GPR54 receptors in vertebrates". *Endocrinology* 150 (2009): 2837-2846.

23. de Roux N., *et al*. "Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54". *Proceedings of the National Academy of Sciences of the United States of America* 100 (2003): 10972-10976.

24. Funes S., *et al*. "The KiSS-1 receptor GPR54 is essential for the development of the murine reproductive system". *Biochemical and Biophysical Research Communications* 312 (2003): 1357-1363.

25. Seminara SB., *et al*. "The GPR54 gene as a regulator of puberty". *The New England Journal of Medicine* 349 (2003): 1614-1627.

26. Ohtaki T., *et al*. "Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor". *Nature* 411 (2001): 613-617.

27. Kotani M., *et al*. "The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54". *Journal of Biological Chemistry* 276 (2001): 34631-34636.

28. Muir AI., *et al*. "AXOR12, a novel human G protein-coupled receptor, activated by the peptide KiSS-1". *Journal of Biological Chemistry* 276 (2001): 28969-28975.

29. Kitahashi T., *et al*. "Cloning and expression of kiss2 in the zebrafish and medaka". *Endocrinology* 150 (2009): 821-831.

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