BIOGRAPHICAL SKETCH

Senior Trainer

NAME: Terasawa, Ei

eRA COMMONS USER NAME (credential, e.g., agency login): ETERASAWA

POSITION TITLE: Professor of Pediatrics and Senior Scientist at the Wisconsin National Primate Research Center, University of Wisconsin

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
University of Tokyo, Tokyo, Japan	B.S.	1961	General Biology
Yokohama City Medical School, Yokohama, Japan	Ph.D.	1966	Medical Physiology
University of California, Berkeley, CA	Postgraduate	1966-67	Physiology
University of California, Los Angeles, CA	Postdoctoral	1967-68	Anatomy

A. Personal Statement

My research focuses on elucidating the mechanism of puberty onset and control of GnRH neuronal function in non-human primates. In primates, 2000 GnRH neurons are scattered widely in the hypothalamus, and they release the decapeptide hormone into the pituitary portal circulation in a pulsatile manner. However, it is very difficult to conduct cellular and molecular studies in primates as, unlike in rodents, GFP-labeled GnRH neurons are not available. To overcome this barrier, I have established a monkey model to study GnRH neurons using a primary cell culture system *in vitro*, and a microdialysis method *in vivo*. Both approaches are powerful, highly technical and unique to the field of Neuroendocrine research. While the microdialysis method allows assessment of the *in vivo* neurosecretion of GnRH, other neuropeptides, neurotransmitters, and neurosteroids directly in the stalk-median eminence under various physiological conditions, GnRH cell cultures derived from the embryonic nasal placode are useful for studying the cellular mechanism of GnRH pulse-generation and the molecular mechanism of steroid hormone action. We have extensively documented that primate GnRH neurons undergo maturational changes with an increase in GnRH mRNA expression along with DNA demethylation of the GnRH gene and an increased release of GnRH peptide. Recently, we are successful in generating GnRH neurons from embryonic and induced pluripotent stem cells. For 4 decades, I have engaged in mentoring a substantial number of graduate students and postdoctoral research fellows, many of which became professors in research universities elsewhere in the world or executives in biotechnology companies in the USA. I also have a passion to promote science education in minority students. I will continue to engage in Pre- and Post-doctoral educations through various T32 supported training programs, such as Endocrinology Reproductive Physiology, Neuroscience, and Pediatrics Fellowship Training programs. I serve on their mentor committees, participating in committee activities, and lead topics of training seminars.

B. Positions and Honors

Position and Employment

1968-1973 Assistant Professor, Dept. of Physiology, Yokohama City University Medical School, Japan.
1973-1980 Associate Scientist, Wisconsin Regional Primate Research Center, University of Wisconsin.
1977-present Member and Trainer, Neuroscience Training Program, University of Wisconsin.
1980-present Senior Scientist, Wisconsin National Primate Research Center, University of Wisconsin.
1991-1999 Chair, Neurobiology Group, Wisconsin National Primate Research Center, Univ. of Wisconsin.
1997-present Professor, Department of Pediatrics, University of Wisconsin.
1997-present Member/Trainer, Endocrinology & Reproductive Physiology Training program, Univ. Wisconsin.
2007-present Co-chair, Neuroscience Working Group, National Primate Research Center, Univ. of Wisconsin.

Other Professional Experience

1987-1991 Member of NIH Study Section (Reproductive Biology)

1991-1994 Member of NIH Study Section (Behavioral Neuroscience)
1990-1993 & 2006-2015 Editorial Board of Neuroendocrinology
1995-1997 Editorial Board of Biology of Reproduction
1998-2002 Council member of the International Society of Neuroendocrinology
2000-2006 Editorial Board of Experimental Biology & Medicine
2003- 2006, 2007-2010 & 2011-2016 Editorial Board of Endocrinology
2004-2009 External Advisory Board for P01 project, University of Michigan
2010-2016 Member of NIH Study Section (Neuroendocrinology, Neuroimmunology, Rhythms, and Sleep)
2015-present Associate Editor of Neuroendocrinology

Reviewer and site visitor for NSF Grants, NICHD RFAs grants (U54 and P01), R01 for NIA, UK MRC grants and fellowship applications, Welcome Trust Fellowship, New Zealand Health Research Council grant, and an *ad hoc* member of the NIH/NINDS Board of Scientific Council. Reviewer for PNAS, Science, Nat Neurosci, J Neurosci, J Neurophysiol, Am J Physiol, Brain Res, Front Neuroendocrinol, Exp Neurol, Mol Cell Neurosci, J Mol Endocr, Clinic Invest, J Physiol, J Comp Neurol, Mol Endocrinol, Neuroendocrinology, J Neuroendocrinol, Cell Tissue Res, Neuroscience, J Reprod Fertil, Brain Res Bull, Physiol & Behav, Life Science, Biochem Biophys Res Comm, Gen Comp, Endocrinology, Steroids, Biol Reprod, Europ J Neurosci, J Neurosci Meth, Psychoneuroendocrinology, Neuropharmacology, Tissue & Cell, Biochem Cell Biol, Trend Endocrinol Metab, Int J Develp Neurosci, J Neurobiol, Peptide, Biochem Cell Biol.

Honors
1967-1968: Ford Foundation Fellow in Anatomy & Neuroendocrinology
1969-1971: Fellowship for Prominent Young Scientist (Japan)
1977-2012: Support from the National Institute of Child Health and Diseases (HD11355)
1981-2011: Support from the National Institute of Child Health and Diseases (HD15433)
1993: University of Wisconsin Chancellor's Award for Excellence in Research
1998: Inaugural Charles H. Sawyer Laureate, UCLA School of Medicine, Los Angeles, CA
2000: Plenary lecturer at the 23rd Annual Meeting of the Japan Neuroscience Society (Yokohama, Japan)
2008: Plenary lecturer at the 85th Annual Meeting of Physiological Society of Japan (Tokyo, Japan)
2002 and 2013: Symposium speaker at the Annual Meetings of the Endocrine Society.
2010: Plenary lecturer at the 7th International Congress of Neuroendocrinology (Rouen, France)
2013: Grand Rounds speaker at Massachusetts General Hospital, Harvard Medical School, Boston, MA
2014: Keynote Speaker at New Zealand Medical Science Congress
2016: Symposium speaker at the International Congress of Endocrinology (Beijing, China)
2018: Symposium speaker at the International Congress of Endocrinology (Cape Town, South Africa)

C. Contribution to Science

AVPV: Neuronal populations responsible for cyclic ovulation in rodent brain:
In 1960-1970 it was believed that neurons in the entire preoptic area or perhaps the suprachiasmatic nucleus (SCN) were responsible for the cyclic ovulation in rats. However, meticulously careful lesion studies in the PI's lab led to finding the foundation for neural circuits responsible for positive feedback effects of ovarian steroids on GnRH neurons. Specifically, lesions of a small periventricular region, located in the preoptic recess of the third ventricle described as the medial preoptic nucleus (MPN), not only disrupt cyclic ovulation in female rats, but also eliminate both the estradiol (E_2) and E_2 plus progesterone (P)-induced LH surges in ovariectomized (OVX) female rats (**a**,**b**,**c**). This is quite a contrast to the role of the SCN. SCN lesions result in persistent estrus, but do not interfere with the E_2+P-induced LH surge, as SCN lesions disrupt only the clock mechanism, not steroid action (**a**,**b**,**c**). Moreover, the size of the MPN is larger in females than males and the MPN does not contain GnRH neurons (**d**). Although later the nomenclature of the MPN was changed to the anterior ventral periventricular nucleus (AVPV), the discovery of kisspeptin further highlights the importance of the MPN/AVPV in regulation of the preovulatory LH/GnRH surge.

- **a.** Wiegand SJ, **Terasawa E**, Bridson WE. Persistent estrus and blockade of progesterone-induced LH release follows lesions which do not damage the suprachiasmatic nucleus. Endocrinology 1978; 102:1645-1648. PMID: 6376071
- **b.** **Terasawa E**, Wiegand SJ, Bridson WE. A role for medial preoptic nucleus on afternoon of proestrus in female rats. Am J Physiol 1980; 238:E533-539. PMID: 7189967

c. Wiegand SJ, **Terasawa E**. Discrete lesions reveal functional heterogeneity of suprachiasmatic structures in regulation of gonadotropin secretion in the female rat. Neuroendocrinology 1982; 34:395-404. PMID: 7069340
d. **Terasawa E**, Davis GA. The LHRH neuronal system in female rats: relation to the medial preoptic nucleus. Endocrinol Jpn 1983; 30:405-417. PMID: 6363049

The role of preovulatory progesterone in GnRH/LH release in non-human primates:

In OVX female rats progesterone (P) is necessary to induce the LH surge and lordosis behavior after treatment with a small priming dose of E_2. In contrast, in primates, it has been believed that E_2 feedback is the only necessary signal for the LH surge, in which E_2 action primarily occurs at the gonadotrope level. In a series of experiments we examined a possible role of P in the LH surge in non-human primates. We found that while a small priming dose of E_2 alone does not induce the LH surge, treatment with P 24 h after E_2 results in the LH surge with a latency of ~60 min (a peak latency of 6 h) and duration of ~12h in OVX monkeys (**a,b**). In fact, the P-induced LH surge is accompanied by an increase in LH pulse-frequency and pulse amplitude (**c**). This stimulatory P action inducing the LH surge requires hypothalamic input, as pentobarbital anesthesia blocks the P action (**a**). Moreover, single unit activity of neurons in the medial basal hypothalamus increases with the P treatment concomitant with the LH surge (**d**) and indeed, P stimulates GnRH release. These findings indicate that P in the presence of E_2 stimulates GnRH/LH release in non-human primates and further suggests that a small rise in P from the dominant follicle at the preovulatory stage gives a signal to the hypothalamus to stimulate the preovulatory GnRH surge. In fact, this hypothesis is proven by another group showing that administration of the P antagonist, RU486, prior to the expected preovulatory gonadotropin surge delays or blocks the preovulatory gonadotropin surge in female monkeys.

a. **Terasawa E**, Noonan J, Bridson WE. Anaesthesia with pentobarbitone blocks the progesterone-induced luteinizing hormone surge in the ovariectomized rhesus monkey. J Endocrinol 1982; 92:327-339. PMID: 7069340
b. **Terasawa E**, Yeoman RR, Schultz NJ. Factors influencing the progesterone-induced luteinizing hormone surge in rhesus monkeys: diurnal influence and time interval after estrogen. Biol Reprod 1984; 31:732-741. PMID: 6542429
c. **Terasawa E**, Krook C, Eman S, Watanabe G, Bridson WE, Sholl SA, Hei DL. Pulsatile luteinizing hormone (LH) release during the progesterone-induced LH surge in the female rhesus monkey. Endocrinology 1987; 120:2265-2271. PMID: 3569132
d. Yeoman RR, **Terasawa E**. An increase in single unit activity of the medial basal hypothalamus occurs during the progesterone-induced luteinizing hormone surge in the female rhesus monkey. Endocrinology 1984; 115:2445-2452. PMID: 6499777

GABA is an inhibitory neurotransmitter before puberty onset in non-human primates:

In old world monkeys and humans, active inhibition of GnRH neurons by the hypothalamus, independent of inhibitory effects of gonadal steroids, during the juvenile hiatal period needs to be removed or reduced prior to the onset of puberty. This phenomenon is unique in primates, as in other species inhibitory effects of circulating gonadal steroids play a major role in suppression of GnRH/LH release during the juvenile period. Extensive studies in PI's lab indicate that the neurotransmitter, gamma amino butyric acid (GABA) is, in part, responsible for neural inhibition of GnRH release prior to puberty onset. The data using push-pull perfusion/ microdialysis methods indicate that GABA release in the stalk-median eminence (S-ME) of prepubertal monkeys is higher than that in pubertal monkeys (reciprocal to pubertal increase in GnRH release). Local infusion of the GABA antagonist, bicuculline, into the stalk-median eminence (S-ME) of prepubertal, but not pubertal monkeys, stimulates GnRH release (**a**), and chronic pulsatile infusion of bicuculline into the S-ME induces precocious menarche and ovulation (**b**). Importantly, blockade of GABA synthesis in the S-ME resulted in an increase in glutamate release, indicating that reduction in GABA stimulates local glutamate release (**c**). Finally, results of a recent study suggest that kisspeptin, a major stimulatory neuromodulator for the pubertal increase in GnRH release, is also inhibited by GABA input in the S-ME of prepubertal monkeys (**d**). The mechanism by which GABA inhibition is removed prior to puberty onset is unknown.

a. Mitsushima D, Hei DL, **Terasawa E**. Gamma-aminobutyric acid is an inhibitory neurotransmitter restricting the release of luteinizing hormone-releasing hormone before the onset of puberty. Proc Natl Acad Sci USA 1994; 91:395-399. PMID: 8278400

b. Keen KL, Burich AJ, Mitsushima D, Kasuya E, **Terasawa E**. Effects of pulsatile infusion of the GABA(A) receptor blocker bicuculline on the onset of puberty in female rhesus monkeys. Endocrinology 1999; 140:5257-5266. PMID: 10537156

c. **Terasawa E**, Luchansky LL, Kasuya E, Nyberg CL. An increase in glutamate release follows a decrease in gamma aminobutyric acid and the pubertal increase in luteinizing hormone releasing hormone release in the female rhesus monkeys. J Neuroendocrinol 1999; 11:275-282. PMID: 10223281

d. Kurian JR, Keen KL, Guerriero KA, **Terasawa E**. Tonic control of kisspeptin release in prepubertal monkeys: implications to the mechanism of puberty onset. Endocrinology 2012; 153:3331-3336. PMCID: PMC3380308

Maturation of non-human primate GnRH neurons:

In primates there are only 2000 GnRH neurons scattered widely in the hypothalamus and they release the decapeptide to the pituitary portal circulation in a pulsatile manner. However, it is very difficult to conduct cellular and molecular studies in primates as, unlike in rodents, GFP-labeled GnRH neurons are not available. To overcome this barrier, the PI established a primary cell culture system of GnRH neurons and proved that GnRH cell cultures derived from the embryonic nasal placode are useful for studying development of primate GnRH neurons, the mechanism of neurosecretion (**a**) and GnRH pulse-generation (**b**,**c**), and the molecular mechanism of steroid hormone action (see next paragraph). Importantly, GnRH neurons derived from nasal placode undergo full maturation *in vitro*, and epigenetic differentiation (increased GnRH gene expression and decreased CpG methylation status) occurs during GnRH neuronal development (**d**).

a. **Terasawa E**, Keen KL, Mogi K, Claude P. Pulsatile release of luteinizing hormone-releasing hormone (LHRH) in cultured LHRH neurons derived from the embryonic olfactory placode of the rhesus monkey. Endocrinology 1999; 140:1432-1441. PMID: 10067872

b. **Terasawa E**, Schanhofer WK, Keen KL, Luchansky L. Intracellular Ca^{2+} oscillations in luteinizing hormone-releasing hormone neurons derived from the embryonic olfactory placode of the rhesus monkey. J Neurosci 1999; 19:5898-5909. PMID: 10407029

c. **Terasawa E**, Keen KL, Grendell RL, Golos TG. Possible role of 5'-adenosine triphosphate in synchronization of Ca^{2+} oscillations in primate luteinizing hormone-releasing hormone neurons. Mol Endocrinol 2005; 19: 2736-2747. PMID: 15994201

d. Kurian JR, Keen KL, **Terasawa E**. Epigenetic changes coincide with i*n vitro* primate GnRH neuronal maturation. Endocrinology 2010; 151:5359-5368. PMCID:PMC2954729

Rapid action of estradiol (E_2) and discovery of neuroestradiol in regulation of GnRH release:

The PI initiated this series of studies to understand the molecular mechanism of estradiol action in primate GnRH neurons. To this end, however, the project led to a completely new finding showing that neuroestradiol, synthesized and released in the S-ME plays a significant role in controlling pulsatile GnRH release. Specifically, we observed that estradiol, rapidly and directly stimulates activity of GnRH neurons *in vitro* leading to GnRH release (**a**,**b**,**c**). Surprisingly, this rapid E_2 action is not mediated through estrogen receptors ERα and ERβ, as it is neither blocked by the ERα and ERβ antagonist, ICI 82,780, nor by cellular knockdown of ERα and ERβ (**c**). Instead, the rapid E_2 action is mediated through the G-protein coupled receptors, GPR30, as cellular knockdown of GPR30 eliminates it *in vitro* (18). Because the rapid stimulatory E_2 action in primates is not described previously, we next examined the effect of E_2 benzoate (EB) *in vivo* using a microdialysis method in OVX females. The results indicate that EB not only rapidly stimulates pulsatile GnRH release, but also E_2 pulsatile release from the S-ME. The peak of the EB-induced E_2 release reaches as high as or higher than the preovulatory E_2 level (**d**). Additionally, E_2 release induced by EB is a consequence of local E_2 synthesized in the S-ME, as simultaneous infusion of the aromatase blocker, letrozole, blocks the EB action (**d**). Finally, a recent study indicates that neuroestradiol appears to play a role in prepubertal suppression of GnRH release. Collectively, neuroestradiol, locally synthesized in the S-ME, appears to participate in regulation of GnRH release from prepubertal stage through mature female reproductive function.

a. Abe H, **Terasawa E**. Firing pattern and rapid modulation of activity by estrogen in primate luteinizing hormone releasing hormone-1 neurons. Endocrinology 2005; 146:4312-4320. PMCID: PMC1479770

b. Noel SD, Keen KL, Baumann DI, Filardo EJ, **Terasawa E.** Involvement of G protein-coupled receptor 30 (GPR30) in rapid action of estrogen in primate LHRH neurons. Mol Endocrinol 2009; 23:349-359. PMCID: PMC2654512

c. Kenealy BP, Kapoor A, Guerriero KA, Keen KL, Garcia JP, Kurian JR, Ziegler TE, **Terasawa E**. Neuroestradiol in the hypothalamus contributes to the regulation of gonadotropin releasing hormone release. J Neurosci 2013; 33:19051-19059. PMCID: PMC3850033

d. Kenealy BP, Keen KL, Garcia JP, Kohlenberg LK, **Terasawa E.** Obligatory role of hypothalamic neuroestradiol during the estrogen-induced LH surge in female ovariectomized rhesus monkeys. Proc Natl Acad Sci USA 2017;114:13804-13809. PMCID: PMC5748216

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40612615/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support:

- 1 R01 HD0489495, Ei Terasawa (PI), July 1, 2018-June 30, 2023
  National Institute of Child Health and Human Development
  Role of Neuroestradiol in Regulation of the GnRH surge: The objective of this grant is to elucidate the critical role of neuroestradiol in GnRH neurosecretion and preovulatory GnRH surge.
- 2R01HD04331, Stephanie Seminara (PI) Ei Terasawa (Subcontract PI), February 1, 2015-Janary 31, 2020
  National Institute of Child Health and Human Development
  Kisspeptin and Neurokinin B: Physiology in Monkey and Pathophysiology in Human: The objective of this grant is to dissect out the relative roles of kisspeptin and neurokinin B in sexual maturation in the human and male rhesus monkey.
- 1 R21 HD092009, Ei Terasawa (PI), April 1, 2017-March 31, 2020 (NCE)
  National Institute of Child Health and Human Development
  Stem Cell-derived GnRH Neurons: Optimization and Characterization**:** The objective of this pilot grant is to characterize GnRH neurons derived from human embryonic and inducible stem cells.

Recently Completed Research Support:

- 1 R21 HD077447, Ei Terasawa (PI), April 1, 2014-March 30, 2016
  National Institute of Child Health and Human Development
  Role of neuroestrogens in control of GnRH release**:** The objective of this grant was to investigate the role of neuroestradiol in regulation of GnRH release.
- 2 R01 HD 15433 (Year 22-26), Ei Terasawa (PI), July 1, 2006-June 30, 2013.
  National Institute of Child Health and Human Development
  Hypothalamic Control of Gonadotropin Secretion: The major goal of this research was to determine the mechanism of GnRH pulse generation and the control of pulsatile GnRH release by ovarian steroid hormones and neurotransmitters in matured animals. During this segment of funding, *in vitro* maturation of GnRH neurons and rapid action of estradiol were determined.
- 2 R01 HD 11355 (Year 23-27), Ei Terasawa (PI), May 15, 2007-April 30, 2014.
  National Institute of Child Health and Human Development
  Hypothalamic Control of Puberty: The goal of this research was to determine the mechanism of puberty onset. During this segment of funding, the role of kisspeptin in regulation of pubertal increase in GnRH was examined.