BIOGRAPHICAL SKETCH

Senior Trainer.

NAME: Jon E. Levine, Ph.D.

eRA COMMONS USER NAME: Jlevine6

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Oberlin College, Oberlin OH	B.A.	1976	Biology, Psychology
University of Illinois, Urbana, IL	Ph.D.	1982	Neuroscience
Oregon National Primate Research Center, and Oregon Health Sciences University, Portland, OR	Postdoctoral	1982-1984	Neuroendocrinology

A. Personal Statement

I assumed the position of Director of the Wisconsin National Primate Research Center as of September 1, 2010, and became a Professor in the Department of Physiology, and subsequently the Department of Neuroscience. I have continued to conduct my research program in two laboratories – one in the Neuroscience Department, and one in the WNPRC – and I continue to serve as a mentor for research faculty, postdoctoral fellows, and graduate students. My research focuses on the actions of steroid hormones in the brain, with particular emphases on the roles that estrogen receptors play in mediating the effects of estradiol on ovulatory cyclicity, reproductive development, and energy homeostasis. I hold NIH grants that support studies in both rodent and non-human primate models of reproductive and metabolic disorders. I continue to collaborate with ERP Faculty such as David Abbott and Ei Terasawa.

I received my own training as a neuroscientist, receiving a Ph.D. in one of the earliest neuroscience training programs at the University of Illinois in 1982. My area of research is neuroendocrinology, with specific interests in the neuroendocrine regulation of reproduction, and in the molecular and cellular actions of steroid hormones in central neurons. I have received continuous funding from the NICHD for my research throughout my 26 years on the faculty in the Department of Neurobiology and Physiology at Northwestern University in Evanston. The training of graduate students in Neuroscience has been an integral part of my research program and my professional pursuits in general, throughout my career. My goal as a ERP preceptor is to continue to mentor graduate students, and provide my input to the training curriculum in neuroendocrine-related classes or seminars, as I have taught classes for undergraduate and graduate students for 26 years in Endocrinology, Neuroendocrinology, Animal Physiology, Mammalian Reproduction, Fundamentals of Neuroscience, and other related areas. I have trained 18 Ph.D. students, with the majority of these having graduated from the Northwestern University Institute for Neuroscience (NUIN). In addition, I have sponsored more than 50 undergraduate honor's research students in the Northwestern Program in the Biological Sciences. I also served as Director of the Program in Biological Sciences for 6 years, and I served as the P.I. and Director of a NIH/NICHD T32 Training Program in Reproductive Sciences for more than 15 years, having renewed this grant for three full 5-year awards.

1. **Dubois SL**, Wolfe A, Radovick S, Boehm U, Levine JE. Estradiol Restrains Prepubertal Gonadotropin Secretion in Female Mice via Activation of ERα in Kisspeptin Neurons. Endocrinology. 2016 Apr;157(4):1546-54. doi: 10.1210/en.2015-1923. Epub 2016 Jan 29. PubMed PMID: 26824364; PubMed Central PMCID: PMC4816723.
2. **Dubois SL**, Acosta-Martínez M, DeJoseph MR, Wolfe A, Radovick S, Boehm U, Urban JH, Levine JE. Positive, but not negative feedback actions of estradiol in adult female mice require estrogen receptor α in kisspeptin neurons. Endocrinology. 2015 Mar;156(3):1111-20. doi: 10.1210/en.2014-1851. Epub 2014 Dec 29. PubMedPMID: 25545386; PubMed Central PMCID: PMC4330313.
3. **Kurian JR,** Louis S, Keen KL, Wolfe A, Terasawa E, Levine JE. The Methylcytosine Dioxygenase Ten-Eleven Translocase-2 (tet2) Enables Elevated GnRH Gene Expression and Maintenance of Male Reproductive Function. Endocrinology. 2016 Sep;157(9):3588-603. doi: 10.1210/en.2016-1087. Epub 2016 Jul 6. PubMed PMID: 27384303; PubMed Central PMCID: PMC5007894.
4. Cikla U, Chanana V, Kintner DB, Udho E, Eickhoff J, Sun W, Marquez S, Covert L, Otles A, Shapiro RA, Ferrazzano P, Vemuganti R, Levine JE, **Cengiz P**. ERα Signaling Is Required for TrkB-Mediated Hippocampal Neuroprotection in Female Neonatal Mice after Hypoxic Ischemic Encephalopathy(1,2,3).

eNeuro. 2016 Jan 28;3(1). pii: ENEURO.0025-15.2015. doi: 10.1523/ENEURO.0025-15.2015. eCollection 2016 Jan-Feb. PubMed PMID: 26839918; PubMed Central PMCID: PMC4731462.

B. Positions and Honors

Positions and Employment

1982-1984	Postdoctoral Fellow, Oregon Regional Primate Research Center, Beaverton, OR
1984-1990	Assistant Professor, Department of Neurobiology & Physiology, Northwestern University, Evanston, IL
1990-1997	Associate Professor, Dept. of Neurobiology & Physiology, Northwestern University
1991- 2010	Director, Training Program in Reproductive Biology, Northwestern University
1999-2005	Director, Program in Biological Sciences, Northwestern University
1997-2010	Professor, Department of Neurobiology & Physiology, Northwestern University
2010 (9/1)	Professor, Department of Neuroscience, University of Wisconsin-Madison
2010 (9/1)	Director, Wisconsin National Primate Research Center, Madison, WI

Other Experience and Professional Appointments

1991-94, 02-07	Editorial Board, *Endocrinology*
1994-2004	Editorial Board, *Endocrine*
1995-1999	NIH/NICHD Population Research Committee Member
1998-2002	Associate Editor, *Endocrinology*
1999-pres.	Editorial Board, *Neuroendocrinology*
1999-pres.	Editorial Board, *Frontiers in Neuroendocrinology*
2002-pres.	Editor-in-Chief, *Frontiers in Neuroendocrinology*

Honors

1985-1986	Eli Lilly Foundation Teaching Scholar
1989-1994	NIH/NICHD Research Career Development Award
1995, 2003	Faculty Teaching Honor Roll, Northwestern University

C. Contribution to Science

1. As a graduate student and a postdoctoral fellow, my early contributions to science stemmed from my work in developing methods for the measurement of hypothalamic neuropeptide release in conscious, freely-moving animals. The control of the reproductive axis by gonadotropin-releasing hormone (GnRH) had been revealed in previous years, but an understanding of the physiological regulation of GnRH neurosecretion had been awaiting a method to examine spontaneous GnRH release profiles in different physiological states, and to monitor alterations in GnRH release to neural and endocrine signals. Using modifications of push-pull perfusion, and then later microdialysis methods, I performed the first measurements and analyses of GnRH release in conscious, unstressed rats, sheep, and monkeys. These experiments demonstrated that GnRH release occurs in rhythmic pulses that are temporally associated with LH pulses, and that the preovulatory LH surge in proestrous rats is evoked by a 2-4h GnRH surge comprised of high-amplitude GnRH pulses. I demonstrated that sequential treatment with estradiol and progesterone evokes a proestrus-like surge of GnRH release, confirming the central actions of progesterone in the stimulation of preovulatory LH surges. These findings opened up future investigations into the roles of estrogen and progesterone receptors in the molecular and cellular events underlying the elaboration of GnRH surges, and hence the maintenance of fertility in female animals. My postdoctoral studies focused on the mechanisms by which steroid hormones exert their positive and negative feedback actions within the reproductive axis. My contribution to the scientific controversy at the time – whether feedback occurs within the primate CNS to control release of preovulatory LH surges – included the finding that estradiol treatment does evoke an increase in GnRH release in ovariectomized rhesus macaques. The physiological role of GnRH surges in women and non-human primates continues to be debated to this day.

a. Levine, J.E. and V.D. Ramirez. (1980) *In vivo* release of luteinizing hormone-releasing hormone estimated with push-pull cannulae from the mediobasal hypothalami of ovariectomized, steroid-primed rats. Endocrinology 107:1782-1790.

b. Levine, J.E. and V.D. Ramirez. (1982) Luteinizing hormone-releasing hormone release during the rat estrous cycle and following ovariectomy as estimated with push-pull cannulae. Endocrinology 111:1439-1448.
c. Levine, J.E., K.F. Pau, V.D. Ramirez, and G.L. Jackson. (1982) Simultaneous measurement of luteinizing hormone-releasing hormone and luteinizing hormone in unanesthetized, ovariectomized sheep. Endocrinology 111:1449-1455.
d. Levine, J.E., R.L. Norman, P.M. Gleissman, T.T. Oyama, and H.G. Spies. (1985) *In vivo* gonadotropin-releasing hormone release and serum luteinizing hormone measurements in ovariectomized, estrogen-treated rhesus macaques. Endocrinology 117:711-721.

2. As a junior faculty member at Northwestern University, much of my work focused on the neuroendocrine systems that convey the negative and positive feedback actions of gonadal steroids, and the mechanisms by which these actions controlled the ovulatory cycle and female fertility. One set of projects examined the possible contribution of neural "GnRH-responsiveness" factors that might be engaged by estrogen and progesterone at mid-cycle and function to heighten gonadotrope sensitivity to GnRH release and thereby amplify the resultant GnRH-induced LH surge. The major contribution of my laboratory was to demonstrate that neuropeptide Y (NPY) neurons serve in this capacity, as they respond to positive feedback-inducing steroid regimens with increased NPY expression and release, and that the actions of NPY through NPY Y1 receptors are required to amplify the GnRH-induced mid-cycle gonadotropin surge. This physiological role for NPY was then confirmed by the demonstration that LH surges are attenuated in NPY null mutant mice.
a. Bauer-Dantoin, A.C., J.H. Urban, and J.E. Levine. (1992) Neuropeptide Y gene expression in the arcuate nucleus is increased during preovulatory luteinizing hormone surges. Endocrinology 131:2953-2958.
b. Leupen, S.L., L.M. Besecke, and J.E. Levine. (1997) Neuropeptide Y Y1 receptor stimulation is required for physiological amplification of preovulatory luteinizing hormone (LH) surges. Endocrinology 138:2735-2739.
c. Xu, M., J. Urban, J. Danforth, and J.E. Levine. (2000) Regulation of neuropeptide Y Y1 receptor gene expression during the estrous cycle: role of progesterone receptors. Endocrinology 141:3319-3327.
d Xu, M., J. Hill, and J.E. Levine. (2000) Attenuation of luteinizing hormone (LH) surges in neuropeptide Y – knockout (NPY-KO) mice. Neuroendocrinology 72:263-271.

3. Classic studies had established that a 24h neural clock governs the release of preovulatory GnRH and LH surges in rodents, and that steroid hormones released by the ripening follicles couple the daily neural signal to the circuitries governing release of GnRH surges. My studies in the late 1990s focused in part on the steroid receptors that mediate this coupling process, and the cellular signaling pathways through which this may occur. Using both mouse and rat models, my laboratory produced a series of papers that provided the foundation for a new model of the cellular mechanisms controlling release of GnRH surges in rodents. The essential elements of this model include the integral role of progesterone receptors ($PR_{A,B}$) in the timing and amplification of GnRH and LH surges, their activation by a ligand-independent mechanism during the initial stages of surge generation, and the particular importance of PRs in coupling the daily neuronal signal to the GnRH surge generating circuitries in the anteroventral periventricular nucleus.
a. Chappell, P.E., J.P. Lydon, O.M. Conneely, B.W. O'Malley, and J.E. Levine. (1997) Endocrine defects in mice carrying a null mutation for the progesterone receptor gene. Endocrinology 138:4147-4153.
b. Chappell, P.E. and J.E. Levine. (2000) Stimulation of GnRH surges by estrogen I: role of progesterone receptors. Endocrinology 141:1477-1485.
c. Chappell, P.E., J. Lee, and J.E. Levine. (2000) Stimulation of GnRH surges by estrogen II: role of cAMP. Endocrinology 141:1486-1492.
d. Chappell, P.E., J. Schneider, P. Kim, and J.E. Levine. (1999) Absence of gonadotropin surges and GnRH self-priming in ovaraiectomized (OVX), estrogen (E2)-treated, progesterone receptor knockout (PRKO) mice. Endocrinology 140: 3653-3658.

4. My laboratory has also contributed to the basic understanding of the neuroendocrine mechanisms governing the onset and course of puberty. It is generally held that puberty is initiated by an increase in the frequency and/or amplitude of GnRH release. This process is, in turn, dependent upon molecular and cellular processes that integrate and convey both central and peripheral signals to the GnRH neurons. Using a refined

microdialysis method, we provided the first direct characterization of the pubertal increase in pulsatile GnRH release in both female and male rats. In more recent work, we have attempted to determine the role that kisspeptin neurons may play in transmitting the signals for the initiation of puberty to the GnRH neurons. In the course of analyzing the physiological roles of ERα in kisspeptin neurons, we determined that these receptors provide a prepubertal brake on the GnRH pulse generator, while also playing a key role in the development of sensitivity to positive feedback in the adult. These studies have called for renewed consideration of the "gonadostat" theory of puberty onset in rodents, wherein reduced sensitivity of kisspeptin neurons to estradiol feedback may contribute to the onset and completion of puberty in females.

a. Sisk, C., H.N. Richardson, P.E. Chappell, and J.E. Levine. (2001) *In vivo* gonadotropin-releasing hormone secretion in female rats during peripubertal development and on proestrus. Endocrinology 142:2929-2936.
b. Harris, G.C. and J.E. Levine. (2003) Pubertal acceleration of pulsatile gonadotropin-releasing hormone release in male rats as revealed by microdialysis. Endocrinology 144:163-171.
c. Mayer C, Acosta-Martinez M, Dubois SL, Wolfe A, Radovick S, Boehm U, Levine JE. Timing and completion of puberty in female mice depend on estrogen receptor alpha-signaling in kisspeptin neurons. Proc Natl Acad Sci U S A. 2010 Dec 28;107(52):22693-8.
d. Dubois SL, Wolfe A, Radovick S, Boehm U, Levine JE. Estradiol Restrains Prepubertal Gonadotropin Secretion in Female Mice via Activation of ERα in Kisspeptin Neurons. Endocrinology. 2016 Apr;157(4):1546-54 PMCID: PMC4816723.

5. Ovarian estrogens exert critically important actions in hypothalamic neurons to regulate ovulatory cyclicity, reproductive behaviors, and energy homeostasis. Estrogen receptor alpha (ERα) appears to mediate most of these effects, as disruption of ERα signaling leads to infertility and metabolic syndrome. ERα signaling mechanisms may include "classical genotropic" effects mediated by direct binding of receptor dimers to DNA, "non-classical genotropic" effects involving tethering of ERs to other transcription factors, and "non-classical non-genotropic" actions mediated by cytoplasmic ERs coupled to membrane-initiated signal transduction pathways. In collaboration with Dr. J. Larry Jameson and Dr. Jeffrey Weiss at Northwestern University, my laboratory has made use of novel ERα mutant mouse models to ascertain the cellular mechanisms by which ERα mediates estradiol (E_2) effects on these physiological. We have utilized a novel mutant ERα knock-in mouse model, which confers non-classical genotropic and non-genotropic signaling in the absence of classical (ERE-dependent) signaling, to determine that non-classical ERα signaling can convey E_2 effects integral to homeostatic feedback control of reproductive hormone secretions, as well as E_2 actions governing body weight regulation.

a. McDevitt MA, Glidewell-Kenney C, Weiss J, Chambon P, Jameson JL, Levine JE. Estrogen response element-independent estrogen receptor (ER)-alpha signaling does not rescue sexual behavior but restores normal testosterone secretion in male ERalpha knockout mice. Endocrinology. 2007 Nov;148(11):5288-94.
b. Zhao Z, Park C, McDevitt MA, Glidewell-Kenney C, Chambon P, Weiss J, Jameson JL, Levine JE. p21-Activated kinase mediates rapid estradiol-negative feedback actions in the reproductive axis. Proc Natl Acad Sci USA. 2009 Apr 28;106(17):7221-6.
c. Gottsch ML, Navarro VM, Zhao Z, Glidewell-Kenney C, Weiss J, Jameson JL, Clifton DK, Levine JE, Steiner RA. Regulation of Kiss1 and dynorphin gene expression in the murine brain by classical and nonclassical estrogen receptor pathways. J Neurosci. 2009 Jul 22;29(29):9390-5. PMCID: PMC2819182.
d. Park CJ, Zhao Z, Glidewell-Kenney C, Lazic M, Chambon P, Krust A, Weiss J, Clegg J, Dunaif A, Jameson JL, Levine JE. Genetic Rescue of Non-classical ERα Signaling Normalizes Energy Balance in Obese ERα-null Mutant Mice. J Clin Invest. 2011 Feb;121(2):604-612.

Complete list of peer-reviewed publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/jon.levine.2/bibliography/48310915/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

5 P51 RR000167 (WNPRC) Mailick, M (PI) 05/01/12 - 04/30/17
NIH/NCRR
Directors Office
These funds support the Director's Office of the Wisconsin Primate Research Center.
Role: Director of the WNPRC

P50 HD44405 Dunaif (PI) 09/01/12 - 06/30/17
NIH/NICHD/ORWH
Genes, Androgens and Intrauterine Environment in PCOS
Project III: Estrogen receptors and metabolic features of PCOS.
This grant supports a Specialized Center of Research entitled "Genes, Androgens, and Intrauterine Environment in PCOS." The projects are designed to investigate the genetic and developmental basis of the pathogenesis of polycystic ovarian syndrome. Project III includes experiments in female marmosets that test the hypothesis that excess androgen exposure leads to the programming of brain tissue to exhibit metabolic features of PCOS in adulthood. The hypothesis specifically holds that androgens program resistance to the metabolic actions of estrogens, giving rise to insulin resistance and other metabolic features of PCOS.
Role: Center Co-Director and PI of Project IV

R01 HD068777-01 (multiple P.I. grant; Levine, Radovick, Hoffman) 09/01/12 - 06/30/17
NIH/NICHD
Sex steroids, kisspeptin, and regulation of GnRH
These studies examine the regulation of kisspeptin and GnRH neurons in the hypothalamus by estrogens. The experiments utilize female mice to test the hypothesis that the positive and negative feedback actions of estradiol on GnRH release are mediated by estrogen receptor alpha activation in anteroventral periventricular and mediobasal hypothalamic kisspeptin neurons, respectively.
Role: P.I. on multiple P.I. grant

2P50 HD028934-21 (Marshall) 04/01/14 – 03/31/19
NIH/NICHD
Clinical and Basic Studies in Polycystic Ovarian Syndrome (RFA-HD-14-017)
Project II: Hypothalamic Steroid Receptors and the Pathogenesis of PCOS
Studies related to this project will make use of viral vector-mediated gene silencing and a validated nonhuman primate model of androgen induced reproductive PCOS phenotypes to address these major gaps in our understanding of the mechanisms that mediate the pathogenesis of PCOS.
Role: P.I., Project II

R21 HD084992-01 (Levine) 04/01/16 – 03/31/18
NIH/NICHD
Neuroestrogen restraint of GnRH in juvenile monkeys
The proposed studies are designed to examine the new hypothesis that neuroestradiol contributes to the prepubertal restraint of GnRH and gonadotropin secretions in juvenile monkeys.
Role: P.I.

Completed Research Support

P01 HD21821 Mayo (PI) 10/01/09 -1 1/30/14
ERalpha signaling in the HPO axis
These studies examine the role of non-classical ERalpha signaling in the negative feedback actions of estrogen in female rodents.
Role: PI on Project II