EDITORIAL

1  Endocrinology at the Beginning of Our Second Century: Connectivity and Conversations
   Teresa K. Woodruff, Editor-in-Chief, Endocrinology

FEATURED ARTICLES

PITUITARY AND NEUROENDOCRINOLOGY

2  Extragonadal Actions of FSH: A Critical Need for Novel Genetic Models
   T. Rajendra Kumar
   Précis: Controversy exists with regard to extra-gonadal actions of FSH. This mini-review summarizes the controversies, identifies the critical gaps, and provides the rationale to develop new genetic models.

REPRODUCTIVE BIOLOGY AND SEX-BASED MEDICINE

9  Identifying the Critical Gaps in Research on Sex Differences in Metabolism Across the Life Span
   Jane E. B. Reusch, T. Rajendra Kumar, Judith G. Regensteiner, and Philip S. Zeitler, on Behalf of the Conference Participants
   Précis: This article highlights major gaps in research addressing sex differences in cardiometabolic disease across the life span, including sex as a biological variable, and suggests future research in this area.

SPECIAL SECTION: DEVELOPMENTAL ORIGINS OF ENDOCRINE DISEASES

MINI-REVIEWS

DEVELOPMENTAL BASIS OF ADULT DISEASE

20  Endocrine Disruptors and Developmental Origins of Nonalcoholic Fatty Liver Disease
   Lindsey S. Treviño and Tiffany A. Katz
   Précis: The references cited in this mini-review were selected from manuscripts found through a PubMed search, without a publication year cutoff. References found in these publications provided additional articles to search and cite.
ENDOCRINE-DISRUPTING CHEMICALS

32 Immune System: An Emerging Player in Mediating Effects of Endocrine Disruptors on Metabolic Health
Amita Bansal, Jorge Henao-Mejia, and Rebecca A. Simmons
Précis: In this review, we focus on studies that demonstrate endocrine-disruptor exposure induces dysfunction of the immune system, which, in turn, has detrimental effects on metabolic health.

STEROID HORMONE ACTIONS

46 Glucocorticoid Signaling in Health and Disease: Insights From Tissue-Specific GR Knockout Mice
Shannon Whirledge and Donald B. DeFranco
Précis: Tissue-specific knockout models have provided insight into the functions of the glucocorticoid receptor. This review examines the reported models, highlighting discoveries in each organ system.

NEUROENDOCRINOLOGY

62 Discovery of GnIH and Its Role in Hypothyroidism-Induced Delayed Puberty
Kazuyoshi Tsutsui, You Lee Son, Mika Kiyohara, and Ichiro Miyata
Précis: This article summarizes the structure and function of gonadotropin-inhibitory hormone (GnIH) in inhibiting reproduction and highlights GnIH action on pubertal disorder induced by thyroid dysfunction.

DEVELOPMENTAL BASIS OF ADULT DISEASE

69 Prenatal Stress, Glucocorticoids, and Developmental Programming of the Stress Response
Patrick O. McGowan and Stephen G. Matthews
Précis: Parental adversity and glucocorticoid exposure can affect multiple generations via both the maternal and paternal lineage. Recent studies have begun to determine mechanisms by which this occurs.

RESEARCH ARTICLES

DIABETES, PANCREATIC AND GASTROINTESTINAL HORMONES

83 Insulin-Deficient Mouse β-Cells Do Not Fully Mature but Can Be Remedied Through Insulin Replacement by Islet Transplantation
Adam Ramzy, Majid Mojibian, and Timothy J. Kieffer
Précis: β-cells from insulin-deficient mice express progenitor markers but lack mature β-cell markers. Insulin replacement by islet transplantation was sufficient for maturation of insulin-deficient β-cells.

ENDOCRINE ORGAN PHYSIOLOGY AND PATHOPHYSIOLOGY

103 Early Endometriosis in Females Is Directed by Immune-Mediated Estrogen Receptor α and IL-6 Cross-Talk
Katherine A. Burns, Seddon Y. Thomas, Katherine J. Hamilton, Steven L. Young, Donald N. Cook, and Kenneth S. Korach
Précis: A mouse model of endometriosis, used to examine the early initiation of disease, revealed that two phases of disease exist—an immune-predominant phase and hormone-predominant phase.

ENDOCRINE-DISRUPTING CHEMICALS

119 Effects of Exposure to the Endocrine-Disrupting Chemical Bisphenol A During Critical Windows of Murine Pituitary Development
Précis: Neonatal BPA exposure alters pituitary Pit1 and Pomp mRNA levels sex specifically. Furthermore, using estrogen receptor–selective agonists, we showed how Pomp can be regulated at the pituitary level.
132 Transgenerational Effects of Bisphenol A on Gene Expression and DNA Methylation of Imprinted Genes in Brain
Zuzana Drobná, Anne D. Henriksen, Jennifer T. Wolstenholme, Catalina Montiel, Philip S. Lambeth, Stephen Shang, Erin P. Harris, Changqing Zhou, Jodi A. Flaws, Mazhar Adli, and Emilie F. Rissman
Précis: Mice were exposed during gestation to BPA and bred to the third filial generation (F3). RNA sequencing, quantitative PCR, and DNA methylation were examined in control vs BPA lineage F3 brains.

ENERGY BALANCE - OBESITY - METABOLISM
145 Neuronal Dnmt1 Deficiency Attenuates Diet-Induced Obesity in Mice
Emily C. Bruggeman, John T. Garretson, Rui Wu, Hang Shi, and Bingzhong Xue
Précis: The present study demonstrates the importance of neuronal DNA methylation in regulating energy homeostasis.

NEUROENDOCRINOLOGY
163 Evolutionally Conserved Function of Kisspeptin Neuronal System Is Nonreproductive Regulation as Revealed by Nonmammalian Study
Mikoto Nakajo, Shinji Kanda, Tomomi Karigo, Akiko Takahashi, Yasuhisa Akazome, Yoshishia Uenoyma, Makito Kobayashi, and Yoshitaka Oka
Précis: Based on multidisciplinary analyses using genetically modified medaka, we suggest that kisspeptin is not involved in HPG axis regulation in nonmammals but regulates various non-GnRH neural systems.

REPRODUCTION, SEX, AND GENDER
184 Notch Signaling Regulates Differentiation and Steroidogenesis in Female Mouse Ovarian Granulosa Cells
Rexxi D. Prasasya and Kelly E. Mayo
Précis: Suppression of Notch signal using siRNA against Jag1 or Rbpj leads to suppression of differentiation and retention of proliferative capacity in mouse granulosa cells.

ADDITIONAL MINI-REVIEWS
PITUITARY AND NEUROENDOCRINOLOGY
199 GnRH Neurons on LSD: A Year of Rejecting Hypotheses That May Have Made Karl Popper Proud
Suzanne M. Moenter
Précis: The Moenter laboratory rejected hypotheses about GnRH neurons many times this year; 2017 was thus a rather good year.

TRANSCRIPTION - GENE REGULATION
206 The Three Ds of Transcription Activation by Glucagon: Direct, Delayed, and Dynamic
Ido Goldstein and Gordon L. Hager
Précis: This review summarizes recent discoveries in glucagon-dependent gene regulation with a focus on transcription factor cross talk.

ADDITIONAL RESEARCH ARTICLES
ADRENAL FUNCTION AND REGULATION
217 Effect of Angiotensin II and ACTH on Adrenal Blood Flow in the Male Rat Adrenal Gland In Vivo
Abdul J. Shah, Tamas Kriska, Kathryn M. Gauthier, John R. Falck, and William B. Campbell
Précis: Angiotensin II and ACTH increase adrenal blood flow in anesthetized rats by release of both nitric oxide and epoxyeicosatrienoic acids or only epoxyeicosatrienoic acids, respectively.
227 Inflammation and Fibrosis in Perirenal Adipose Tissue of Patients With Aldosterone-Producing Adenoma
Chunyan Wu, Huijian Zhang, Jiajun Zhang, Cuihua Xie, Cunxia Fan, Hongbin Zhang, Peng Wu, Qiang Wei, Wanlong Tan, Lingling Xu, Ling Wang, Yaoming Xue, and Meiping Guan
Précis: Our results demonstrate perirenal adipose tissue dysfunction, inflammation, and fibrosis in patients with APA. In vitro experiments further confirmed the effect of aldosterone on human adipose cells.

238 Obligatory Metabolism of Angiotensin II to Angiotensin III for Zona Glomerulosa Cell–Mediated Relaxations of Bovine Adrenal Cortical Arteries
Précis: To stimulate zona glomerulosa cells to release epoxyeicosatrienoic acids and cause adrenal artery relaxation, angiotensin II must be metabolized by an aminopeptidase to angiotensin III.

248 Regeneration of Functional Adrenal Tissue Following Bilateral Adrenalectomy
Précis: Several weeks following complete ADX in rats, functional foci of adrenocortical tissue developed in the peritoneal cavity, reestablishing baseline and stress levels of corticosterone and aldosterone.

CALCIUM METABOLISM - BONE
260 Sclerostin Antibody Reverses Bone Loss by Increasing Bone Formation and Decreasing Bone Resorption in a Rat Model of Male Osteoporosis
Xiaodong Li, Michael S. Ominsky, Kelly S. Villasenor, Qing-Tian Niu, Frank J. Asuncion, Xuechun Xia, Mario Grisanti, Thomas J. Wronski, W. Scott Simonet, and Hua Zhu Ke
Précis: In an osteopenic, orchietomized rat model, sclerostin antibody for 6 weeks restored bone mass and strength by increasing bone formation and decreasing bone resorption.

272 β-Catenin Directs Long-Chain Fatty Acid Catabolism in the Osteoblasts of Male Mice
Julie L. Frey, Soohyun P. Kim, Zhu Li, Michael J. Wolfgang, and Ryan C. Riddle
Précis: This study demonstrates that Wnt-generated signals regulate fatty acid utilization by the osteoblast via a canonical mechanism requiring the transcription factor β-catenin.

CANCER - ONCOGENES
285 Upregulation of IRS1 Enhances IGF1 Response in Y537S and D538G ESR1 Mutant Breast Cancer Cells
Zheqi Li, Kevin M. Levine, Amir Bahreini, Peilu Wang, David Chu, Ben Ho Park, Steffi Oesterreich, and Adrian V. Lee
Précis: In genome-edited Y537S and D538G ESR1 mutation breast cancer cells, upregulation of multiple IGF signaling intermediary genes, including IRS, enhances growth response and downstream signaling.

ENDOCRINE ORGAN PHYSIOLOGY AND PATHOPHYSIOLOGY
297 Functional Characterization of MicroRNA-27a-3p Expression in Human Polycystic Ovary Syndrome
Mingming Wang, Jing Sun, Bo Xu, Marcin Chrusciel, Jun Gao, Maciej Bazert, Joanna Stelmaszewska, Yunyun Xu, Hongwen Zhang, Leszek Pawelczyk, Fei Sun, Suk Ying Tsang, Nafs Rahman, Slawomir Wolczyński, and Xiangdong Li
Précis: A functional role was identified for the upregulated miR-27a-3p expression in the observed granulosa cell dysfunction in patients with PCOS.

ENERGY BALANCE - OBESITY - METABOLISM
310 Glucocorticoids Suppress the Browning of Adipose Tissue via miR-19b in Male Mice
Yi-Fan Ly, Jing Yu, Yun-Lu Sheng, Min Huang, Xiao-Cen Kong, Wen-Juan Di, Juan Liu, Hong Zhou, Hui Liang, and Guo-Xian Ding
Précis: GCs regulate miR-19b expression. Gain- and loss-of-function analysis proved that DEX suppresses the browning of adipose tissue and BAT function via transcriptionally regulating miR-19b expression.
Male Brown Fat–Specific Double Knockout of IGFIR/IR: Atrophy, Mitochondrial Fission Failure, Impaired Thermogenesis, and Obesity
Vanessa Viana-Huete, Carlos Guillén, Gema García, Silvia Fernández, Ana García-Aguilar, C. R. Kahn, and Manuel Benito
Précis: The lack of IGFIR/IR receptors in brown fat induces atrophy, impairs thermogenic mechanisms, and triggers obesity susceptibility. Upon consumption of a high-fat diet, DKO mice show manifest obesity.

Selective Pharmacogenetic Activation of Catecholamine Subgroups in the Ventrolateral Medulla Elicits Key Glucoregulatory Responses
Ai-Jun Li, Qing Wang, and Sue Ritter
Précis: Selective activation of C1 catecholamine neurons in the ventrolateral medulla is sufficient to increase blood glucose, corticosterone levels, and feeding in the absence of glucoprivation.

The Absence of Laminin α4 in Male Mice Results in Enhanced Energy Expenditure and Increased Beige Subcutaneous Adipose Tissue
Marcella K. Vačík, Alen Blagajcevic, Honggang Ye, Mallory C. Morse, Feipeng Yang, Anna Goddi, Eric M. Brey, and Ronald N. Cohen
Précis: Despite similar food consumption and activity, mice lacking basement membrane protein laminin α4 were resistant to obesity and had increased beige subcutaneous adipose tissue and energy expenditure.

The Hypothalamic Inflammatory/Gliosis Response to Neonatal Overnutrition Is Sex and Age Dependent
Pilar Argente-Arizón, Francisca Díaz, Purificación Ros, Vicente Barrios, Manuel Tena-Sempere, Luis Miguel García-Segura, Jesús Argente, and Julie A. Chowen
Précis: Neonatal overnutrition increases serum triglyceride and fatty acid levels, as well as hypothalamic TNFα levels, activating a hypothalamic inflammatory process in adult males but not females.

NEUROENDOCRINOLOGY

Desacyl Ghrelin Decreases Anxiety-like Behavior in Male Mice
Parinaz Mahbod, Eric P. Smith, Maureen E. Fitzgerald, Rachel L. Morano, Benjamin A. Packard, Sriparna Ghosal, Jessie R. Scheiman, James P. Herman, and Jenny Tong
Précis: We investigated the role of acylated and desacyl ghrelin in regulation of anxiety-related behavior in mice. Desacyl ghrelin inhibits anxiety-like behavior in the central nervous system.

Dietary Manipulations That Induce Ketosis Activate the HPA Axis in Male Rats and Mice: A Potential Role for Fibroblast Growth Factor-21
Précis: Inducing dietary ketosis by two distinct mechanisms (one acute and one chronic) results in HPA axis activation, and these HPA effects are attenuated in mice that lack FGF21.

Estradiol-Dependent Stimulation and Suppression of Gonadotropin-Releasing Hormone Neuron Firing Activity by Corticotropin-Releasing Hormone in Female Mice
Chayarndorn Phumsatitpong and Suzanne M. Moenter
Précis: CRH exerts both stimulatory and inhibitory effects on GnRH neuron firing activity via activation of different receptors in an estradiol-dependent manner.

Pubertal Escape From Estradiol Negative Feedback in Ewe Lambs Is Not Accounted for by Decreased ESR1 mRNA or Protein in Kisspeptin Neurons
Michelle N. Bedenbaugh, Marcella D’Oliveira, Rodolfo C. Cardoso, Stanley M. Hileman, Gary L. Williams, and Marcel Amstalden
Précis: Changes in the expression of ESR1 in kisspeptin neurons do not explain the pubertal escape from estradiol negative feedback in ewe lambs.

Sim1 Neurons Are Sufficient for MC4R-Mediated Sexual Function in Male Mice
Erin Semple and Jennifer W. Hill
Précis: tbMC4R null mice show sexual dysfunction with an inability to ejaculate. Expressing MC4R only on Sim1 neurons restored these deficits, implicating these neurons in the regulation of sexual function.
Testosterone and Corticosterone in the Mesocorticolimbic System of Male Rats: Effects of Gonadectomy and Caloric Restriction

Précis: Rats were GDX and calorie restricted for 2 or 6 weeks; testosterone was present in mesocorticolimbic nodes after GDX, as were steroidogenic enzymes, which suggest local steroidogenesis.

PITUITARY AND NEUROENDOCRINOLOGY

Prenatal High Estradiol Exposure Induces Sex-Specific and Dietarily Reversible Insulin Resistance Through Decreased Hypothalamic INSR
Hui-Hui Wang, Cheng-Liang Zhou, Min Lv, Qian Yang, Ju-Xue Li, Min Hou, Jing Lin, Xin-Mei Liu, Yan-Ting Wu, Jian-Zhong Sheng, and He-Feng Huang

Précis: Human offspring of fresh ET showed elevated insulin and HOMA-IR scores. Chronic food restriction reversed the insulin resistance of HE mice by rescuing the decreased hypothalamic INSR.

REPRODUCTION, SEX, AND GENDER

Epigenetic Therapy: Novel Translational Implications for Arrest of Environmental Dioxin-Induced Disease in Females
Zaraq Khan, Ye Zheng, Tiffany L. Jones, Abigail A. Delaney, Luiz F. Correa, Chandra C. Shenoy, Kashayarsha Khazaei, and Gaurang S. Daftary

Précis: KLF11 antagonized TCDD-mediated endometriotic progression and fibrosis via differential regulation of metabolic enzyme CYP3A4, providing translational implications for environmentally induced disease.

Prostaglandin-Endoperoxide Synthase 1 Mediates the Timing of Parturition in Mice Despite Unhindered Uterine Contractility
Jennifer L. Herington, Christine O’Brien, Michael F. Robuck, Wei Lei, Naoko Brown, James C. Slaughter, Bibhash C. Paria, Anita Mahadevan-Jansen, and Jeff Reese

Précis: The current study investigated whether impaired luteolysis, and consequent increased progesterone levels at term pregnancy, was solely responsible for the delayed parturition phenotype of Ptgs1-knockout mice.

The Endometrial Polarity Paradox: Differential Regulation of Polarity Within Secretory-Phase Human Endometrium
Sarah Whitby, Lois A. Salamonsen, and Jemma Evans

Précis: Endometrial polarity determinants are differentially regulated within cellular compartments as the menstrual cycle progresses. Endometrial polarity changes are hormonally regulated.

SIGNALING

Glucocorticoid Receptor Signaling Impairs Protein Turnover Regulation in Hypoxia-Induced Muscle Atrophy in Male Mice

Précis: Skeletal muscle GR deficiency in mice resolved reduced food intake–mediated muscle atrophy but not under hypoxic conditions. GR is important for altered hypoxia-induced protein turnover signaling.

STEROID HORMONE ACTIONS

Selective Glucocorticoid Receptor Antagonist CORT125281 Activates Brown Adipose Tissue and Alters Lipid Distribution in Male Mice
Jan Kroon, Lisa L. Koornneef, Jose K. van den Heuvel, Cristy R. C. Verzijl, Nienke M. van de Veld, Isabel M. Mol, Hetty C. M. Sips, Hazel Hunt, Patrick C. N. Rensen, and Onno C. Mejers

Précis: Glucocorticoid receptor blockade by treatment with selective antagonist CORT125281 activates brown adipose tissue, prevents weight gain, reduces fat mass, and lowers plasma lipid levels in male mice.

Topical 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibition Corrects Cutaneous Features of Systemic Glucocorticoid Excess in Female Mice
Ana Tiganescu, Melanie Hupe, Yoshikazu Uchida, Theadora Mauro, Peter M. Elias, and Walter M. Holleran

Précis: Topical 11β-hydroxysteroid dehydrogenase type 1 inhibition normalizes steroid-induced skin thinning, epidermal integrity, poor healing, and gene dysregulation despite ongoing systemic steroid exposure.
T3 and Glucose Coordinately Stimulate ChREBP-Mediated Ucp1 Expression in Brown Adipocytes From Male Mice
Liora S. Katz, Shiliyang Xu, Kai Ge, Donald K. Scott, and Marvin C. Gershengorn

Précis: T3 and glucose coordinately upregulate Ucp1 and mitochondrial biogenesis in brown adipocytes, and ChREBP is a main mediator of this response.

ENDOCRINE SOCIETY

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