Published in final edited form as:

Int J Dev Neurosci. 2013 October ; 31(6): 448–451. doi:10.1016/j.ijdevneu.2013.03.004.

Developmental Regulation of Neuronal Genes by DNA Methylation: Environmental Influences

Melinda E. Wilson* and Tomoko Sengoku

Department of Physiology, College of Medicine, University of Kentucky, Lexington, KY 40536

Abstract

Steroid hormones have wide-ranging organizational, activational and protective actions in the brain. In particular, the organizational effects of early exposure to 17 β -estradiol (E2) and glucocorticoids are essential for long-lasting behavioral and cognitive functions. Both steroid hormones mediate many of their actions through intracellular receptors that act as transcription factors. In the rodent cerebral cortex, estrogen receptor mRNA and protein expression are high early in postnatal life and declines dramatically as the animal approaches puberty. An understanding of the molecular mechanisms driving this developmental regulation of gene expression is critical for understanding the complex events that determine lasting brain physiology and prime the plasticity of neurons. Gene expression can be suppressed by the epigenetic modification of the promoter regions by DNA methylation that results in gene silencing. Indeed, the decrease in ER α mRNA expression in the cortex during development is accompanied by an increase in promoter methylation. Numerous environmental stimuli can alter the DNA methylation that occurs for ER α , glucocorticoid receptors, as well as many other critical genes involved in neuronal development. For example, maternal behavior towards pups can alter epigenetic regulation of ER α mRNA expression. Additionally perinatal stress and exposure to environmental estrogens can also have lasting effects on gene expression by modifying DNA methylation of these important genes. Taken together, there appears to be a critical window during development where, outside factors that alter epigenetic programming can have lasting effects on neuronal gene expression.

Introduction

Steroid hormones play a crucial role in coordinating many neuroendocrine events that control sexual development, sexual behavior and reproduction. 17 β -estradiol is the primary biologically active form of estrogen and in rodents, it is critical for sexual differentiation of the brain (see review by (McCarthy 2008)). For example, estradiol organizes neural circuits and regulates apoptosis of neurons leading to long-term differences in the male and female brain (Toran-Allerand 1976; Anderson, Fleming et al. 1986; Rhees, Shryne et al. 1990). Many of the physiological effects of estrogen are mediated primarily by two intracellular receptors, ER α and ER β (Green, Walter et al. 1986; Koike, Sakai et al. 1987; White, Lees et al. 1987; Kuiper, Enmark et al. 1996; Mosselman, Polman et al. 1996). Both ER α and ER β are expressed in neurons and glia (Donahue, Stopa et al. 2000; Chaban, Lakhter et al. 2004),

© 2013 ISDN. Published by Elsevier Ltd. All rights reserved.

Address correspondence and reprint requests to: Dr. Melinda E. Wilson, Department of Physiology, University of Kentucky College of Medicine, 800 Rose Street, Lexington, KY 40536, Phone: (859) 323-9618, Fax: (859) 323-1070, melinda.wilson@uky.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and both are expressed throughout the brain with distinct patterns in different brain regions and with differing levels of expression during development (Shughrue, Lane et al. 1997; Osterlund, Grandien et al. 2000; Osterlund, Gustafsson et al. 2000; Gonzalez, Cabrera-Socorro et al. 2007; Prewitt 2007). Estrogen action in the cortex may play a role in regulating learning and memory (McEwen and Alves 1999; Simpkins and Singh 2008) and contribute to sex differences observed therein.

Glucocorticoids also play an important role in establishing the neonatal brain's life-long response to stress. In particular glucocorticoid receptor (GR) expression in the hippocampus and amygdala are crucial for regulating stress and anxiety (Herman, McKlveen et al. 2012). Thus, an understanding of the regulation of steroid hormone receptors in non-reproductive brain regions such as the cortex and hippocampus is a critical, yet understudied area. In this manuscript we will review some of what is known about the mechanisms of normal developmental regulation of ER α mRNA as well as factors that can disrupt this regulation of ER α and GR.

The regulation of gene expression by epigenetic modification is an emerging mechanism for controlling neuronal gene expression (for review see (Takizawa and Meshorer 2008) and (Mehler 2008). Epigenetic modification of chromatin involves changes to DNA bases and the associated proteins in the absence of changes in the DNA sequence. Epigenetic modifications can include histone acetylation, histone methylation and DNA methylation (Wolffe 1998). All of these modifications can contribute to lasting changes in gene expression and can be associated with either gene repression or gene expression. In this review we will primarily focus on the gene suppression by DNA methylation. The first step in DNA methylation results in the enzymatic transfer of a methyl group to the 5'-position of the pyrimidine ring of a cytosine residue followed by a guanine (CpG dinucleotides). DNA methyltransferase 3A (DNMT3A) initiates this modification and it is maintained by DNMT1 (Klose and Bird 2006). CpG residues are often found upstream or downstream of the transcriptional start site. These methylated cytosines direct DNA methyl binding proteins such as methyl binding domain proteins 1, 2, 3, 4 and MeCP2 (Nan, Ng et al. 1998; Ng, Zhang et al. 1999; Ng, Jeppesen et al. 2000) which can induce histone deacetylases and suppress transcription. Epigenetic modification of chromatin in neurons has, indeed, been shown to play an important role in regulating gene expression during neuronal development and in learning and memory (Levenson and Sweatt 2005; Kiefer 2007; Day and Sweatt 2011; Guo, Ma et al. 2011). MeCP2 gene mutations are also the cause of some cases of Rett syndrome, a progressive neurological developmental disorder that appears during early childhood when sensory experience is driving the synaptic reorganization required for creating mature circuits in the brain (Zoghbi 2003) (Guy, Hendrich et al. 2001). Additionally, MeCP2 is differentially expressed in the hypothalamus during a critical time in sexual differentiation of the brain (Kurian, Bychowski et al. 2008). Furthermore, DNMT3 expression has also been shown to be dynamically regulated in the developing brain as well as in the adult cortex (Feng, Chang et al. 2005; Siegmund, Connor et al. 2007; Westberry, Trout et al. 2010). These correlative changes suggest that DNA methylation may be involved in determining the expression pattern of neuronal genes during neuronal development.

Developmental regulation of estrogen receptor-alpha mRNA

One example of a neuronal gene that is developmentally regulated during brain development is the estrogen receptor alpha (ER α) gene. Both ER α protein and mRNA levels change dramatically during postnatal brain development (Simerly, Chang et al. 1990; Toran-Allerand, Miranda et al. 1992; Shughrue, Lane et al. 1997). High levels of estradiol binding in non-hypothalamic regions such as the cortex and hippocampus are apparent during the

first two weeks of life (Pfaff and Keiner 1973; Sheridan 1979; Shughrue, Stumpf et al. 1990). This expression, however, declines as animals approach puberty. In rats and mice, ER α mRNA expression was shown to correlate with the changes in estrogen binding in the hippocampus and cortex (O'Keefe, Li et al. 1995; Prewitt 2007). Furthermore, when either fetal rat hippocampal or cortical tissue was transplanted to the brain of a neonatal animal, the developmental profile of ER α mRNA expression in the transplants continued with the profile of the age of the donor (O'Keefe, Pedersen et al. 1993), suggesting that the control of ER α gene expression is programmed in the developing tissue itself and does not rely on cues from the surrounding tissue.

To investigate such additional potential mechanisms regulating this decline in ER α mRNA expression across early postnatal development, we examined the methylation status of the ER α promoter. We have observed that several of the promoters of the mouse ER α gene become progressively methylated beginning at postnatal day 10 (Westberry, Trout et al. 2010). This age corresponds with the beginning of the decline in ER α mRNA expression in the cortex. Furthermore, chromatin immunoprecipitation assays determined that the methyl-DNA binding protein, MeCP2, is associated with this promoter at the same time it becomes methylated. These observations suggest that methylation does play a role in the suppression of ER α mRNA in the developing brain and that the ER α promoter is a target of MeCP2 activity. Additionally we examined the expression pattern of the *de novo* DNMT, DNMT3A, in the isocortex, prefrontal cortex and hippocampus. A gradual increase with age was observed in DNMT3A mRNA expression (Westberry, Trout et al. 2010).

ER α is also developmentally regulated by epigenetic modification in other areas of the brain normally associated with reproduction, such as the preoptic area of the hypothalamus. Auger and colleagues have shown that ER α mRNA expression is higher in females as compared to males and there is a corresponding decrease in methylation of the ER α promoter (Kurian, Olesen et al. 2010). Furthermore, they and others have demonstrated a developmental sex difference in DNMT expression in the hypothalamus, suggesting not only are epigenetic mechanisms regulation important in development, but in generating sex differences gene expression as well (McCarthy, Auger et al. 2009).

Environmental influences on epigenetic regulation of steroid hormone receptor gene expression

Stress

The normal developmental process of gene expression that is intrinsically controlled is susceptible to disruption by many outside influences. Maternal care during the first two weeks of life in rodent provides lasting influence during this critical window in brain development. Meaney and colleagues were the first to demonstrate that maternal behavior could alter gene expression by modifying chromatin (Weaver, Cervoni et al. 2004). They observed that there were two types of maternal behaviors: high-licking and low-licking grooming that could alter gene expression and behavior in their offspring (Liu, Diorio et al. 1997; Champagne, Francis et al. 2003). Pups with high-licking mothers tended to have a lower stress response as adults, along with increased glucocorticoid receptor (GR) expression in the hippocampus. These changes in gene expression were also shown to be accompanied by epigenetic modifications in the promoter for the glucocorticoid receptor gene. In the high-lick offspring where GR mRNA expression was increased, the promoter was less methylated when compared to low-lick offspring (Weaver, Cervoni et al. 2004). Additionally, associated with maternal behavior towards offspring, prenatal stressors have also been shown to alter DNA methylation patterns and neuronal gene expression leading to lasting effects into adulthood (Goel and Bale 2007). Bale and colleagues have demonstrated

that varied stress *in utero* could lead to changes in corticotrophin releasing factor and GR expression associated with alterations in promoter methylation in the hypothalamus and amygdala (Mueller and Bale 2008). These changes were correlated with depressed behavioral response to several stressors in male offspring as adults.

In addition to the GR promoter, the ER α promoter was shown to also be susceptible to changes in DNA methylation caused by maternal grooming (Champagne, Weaver et al. 2006). Female offspring from high-licking mothers had lower levels of promoter methylation of ER α in the hypothalamus corresponding with the increased expression of ER α mRNA. These changes are maintained in adulthood and associated with similar grooming activities in the females when they care for pups (Francis, Diorio et al. 1999). Additionally, altered ER α expression and methylation is also associated with altered lordosis behaviors where low-lick females are more responsive to males (Cameron, Shahrokh et al. 2008). Taken together, either prenatal or postnatal exposure to stress can have lasting effects on gene expression and behaviors in the offspring that appear to be mediated by DNA methylation.

Endocrine disruptors

Exposure to environmental toxins can have wide ranging teratogenic effects in developing animals. In particular, estrogenic compounds from plastics found in the environment, such as bisphenol A (BPA), can have numerous negative effects on multiple tissues depending on the dose, length, and timing of exposure (Rubin 2011). While studies in humans have been mostly correlative, direct effects of BPA exposure have been shown to have a variety of adverse effects in rodents. In particular BPA exposure in the developing fetus or neonate can alter the timing of puberty (Howdeshell, Hotchkiss et al. 1999; Honma, Suzuki et al. 2002), alter estrous cycles (Rubin, Murray et al. 2001; Monje, Varayoud et al. 2010), cause prostate neoplasia (Prins, Birch et al. 2007), alter mammary gland development (Markey, Luque et al. 2001; Vandenberg, Maffini et al. 2008) and alter aggressive and cognitive behaviors (Kawai, Nozaki et al. 2003; Tian, Hwan Kim et al. 2011). BPA exposure of female rats during the first week of life results in lower ER α mRNA levels in the medial preoptic area and ventromedial nucleus of the hypothalamus (Monje, Varayoud et al. 2007). This suppression is also associated with a disruption in gonadotropin releasing hormone production, potentially leading to reproductive deficits (Monje, Varayoud et al. 2010). Furthermore, BPA exposure *in utero* results in alterations in global methylation patterns of genes expressed in the forebrains of exposed mice which could potentially lead to far-reaching negative consequences in behavior and cognition (Yaoi, Itoh et al. 2008). These results again demonstrate that there is a critical window of coordinated neuronal gene expression that is susceptible to environmental factors that alter DNA methylation. These changes can potentially lead to lasting changes in gene expression and behavior in adulthood.

Summary

Coordinated regulation of the steroid hormone receptor genes is critical for mediating the response to hormones in an age, gender, and brain region-specific manner. In this review we have touched upon several physiological and environmental influences that can alter the expression of the estrogen receptor and glucocorticoid receptor genes in the cortex, hippocampus and hypothalamus by DNA methylation. A deeper understanding of these mechanisms will ultimately lead to our understanding of the molecular mechanisms underlying how gene expression in the brain develops and ultimately, how neuronal genes respond to neuronal insults associated with injury, neurodegeneration or normal aging.

Acknowledgments

This work cited from our laboratory was supported by the National Science Foundation (NSF IOS0919944 and NSF IOS1121129) (MEW) and COBRE grant P20 RR15592 from the National Center for Research Resources (NCRR). All opinions, findings and conclusions expressed in this material are those of the authors and not those necessarily of NSF or NCRR.

References

- Anderson RH, Fleming DE, et al. Relationships between sexual activity, plasma testosterone, and the volume of the sexually dimorphic nucleus of the preoptic area in prenatally stressed and non-stressed rats. *Brain Res.* 1986; 370(1):1–10. [PubMed: 3518858]
- Cameron NM, Shahrokh D, et al. Epigenetic programming of phenotypic variations in reproductive strategies in the rat through maternal care. *J Neuroendocrinol.* 2008; 20(6):795–801. [PubMed: 18513204]
- Chaban VV, Lakhter AJ, et al. A Membrane Estrogen Receptor Mediates Intracellular Calcium Release in Astrocytes. *Endocrinology.* 2004
- Champagne FA, Francis DD, et al. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. *Physiol Behav.* 2003; 79(3):359–371. [PubMed: 12954431]
- Champagne FA I, Weaver C, et al. Maternal care associated with methylation of the estrogen receptor- α 1b promoter and estrogen receptor- α expression in the medial preoptic area of female offspring. *Endocrinology.* 2006; 147(6):2909–2915. [PubMed: 16513834]
- Day JJ, Sweatt JD. Epigenetic mechanisms in cognition. *Neuron.* 2011; 70(5):813–829. [PubMed: 21658577]
- Donahue JE, Stopa EG, et al. Cells containing immunoreactive estrogen receptor- α in the human basal forebrain. *Brain Res.* 2000; 856(1–2):142–151. [PubMed: 10677621]
- Feng J, Chang H, et al. Dynamic expression of de novo DNA methyltransferases Dnmt3a and Dnmt3b in the central nervous system. *J Neurosci Res.* 2005; 79(6):734–746. [PubMed: 15672446]
- Francis D, Diorio J, et al. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science.* 1999; 286(5442):1155–1158. [PubMed: 10550053]
- Goel N, Bale TL. Identifying early behavioral and molecular markers of future stress sensitivity. *Endocrinology.* 2007; 148(10):4585–4591. [PubMed: 17640992]
- Gonzalez M, Cabrera-Socorro A, et al. Distribution patterns of estrogen receptor α and β in the human cortex and hippocampus during development and adulthood. *J Comp Neurol.* 2007; 503(6):790–802. [PubMed: 17570500]
- Green S, Walter P, et al. Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A. *Nature.* 1986; 320(6058):134–139. [PubMed: 3754034]
- Guo JU, Ma DK, et al. Neuronal activity modifies the DNA methylation landscape in the adult brain. *Nat Neurosci.* 2011; 14(10):1345–1351. [PubMed: 21874013]
- Guy J, Hendrich B, et al. A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. *Nat Genet.* 2001; 27(3):322–326. [PubMed: 11242117]
- Herman JP, McKlveen JM, et al. Neural regulation of the stress response: glucocorticoid feedback mechanisms. *Braz J Med Biol Res.* 2012; 45(4):292–298. [PubMed: 22450375]
- Honma S, Suzuki A, et al. Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. *Reprod Toxicol.* 2002; 16(2):117–122. [PubMed: 11955942]
- Howdeshell KL, Hotchkiss AK, et al. Exposure to bisphenol A advances puberty. *Nature.* 1999; 401(6755):763–764. [PubMed: 10548101]
- Kawai K, Nozaki T, et al. Aggressive behavior and serum testosterone concentration during the maturation process of male mice: the effects of fetal exposure to bisphenol A. *Environ Health Perspect.* 2003; 111(2):175–178. [PubMed: 12573901]
- Kiefer JC. Epigenetics in development. *Dev Dyn.* 2007; 236(4):1144–1156. [PubMed: 17304537]
- Klose RJ, Bird AP. Genomic DNA methylation: the mark and its mediators. *Trends Biochem Sci.* 2006; 31(2):89–97. [PubMed: 16403636]

- Koike S, Sakai M, et al. Molecular cloning and characterization of rat estrogen receptor cDNA. *Nucleic Acids Res.* 1987; 15(6):2499–2513. [PubMed: 3031601]
- Kuiper GG, Enmark E, et al. Cloning of a novel receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci U S A.* 1996; 93(12):5925–5930. [PubMed: 8650195]
- Kurian JR, Bychowski ME, et al. Mecp2 Organizes Juvenile Social Behavior in a Sex-Specific Manner. *J Neurosci.* 2008; 28(28):7137–7142. [PubMed: 18614683]
- Kurian JR, Olesen KM, et al. Sex differences in epigenetic regulation of the estrogen receptor- α promoter within the developing preoptic area. *Endocrinology.* 2010; 151(5):2297–2305. [PubMed: 20237133]
- Levenson JM, Sweatt JD. Epigenetic mechanisms in memory formation. *Nat Rev Neurosci.* 2005; 6(2):108–118. [PubMed: 15654323]
- Liu D, Diorio J, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science.* 1997; 277(5332):1659–1662. [PubMed: 9287218]
- Markey CM, Luque EH, et al. In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. *Biol Reprod.* 2001; 65(4):1215–1223. [PubMed: 11566746]
- McCarthy MM. Estradiol and the developing brain. *Physiol Rev.* 2008; 88(1):91–124. [PubMed: 18195084]
- McCarthy MM, Auger AP, et al. The epigenetics of sex differences in the brain. *J Neurosci.* 2009; 29(41):12815–12823. [PubMed: 19828794]
- McEwen BS, Alves SE. Estrogen actions in the central nervous system. *Endocr Rev.* 1999; 20(3):279–307. [PubMed: 10368772]
- Mehler MF. Epigenetic principles and mechanisms underlying nervous system functions in health and disease. *Prog Neurobiol.* 2008; 86(4):305–341. [PubMed: 18940229]
- Monje L, Varayoud J, et al. Neonatal exposure to bisphenol A modifies the abundance of estrogen receptor α transcripts with alternative 5'-untranslated regions in the female rat preoptic area. *J Endocrinol.* 2007; 194(1):201–212. [PubMed: 17592034]
- Monje L, Varayoud J, et al. Exposure of neonatal female rats to bisphenol A disrupts hypothalamic LHRH pre-mRNA processing and estrogen receptor α expression in nuclei controlling estrous cyclicity. *Reprod Toxicol.* 2010; 30(4):625–634. [PubMed: 20951796]
- Mosselman S, Polman J, et al. ER β : identification and characterization of a novel human estrogen receptor. *FEBS Lett.* 1996; 392(1):49–53. [PubMed: 8769313]
- Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. *J Neurosci.* 2008; 28(36):9055–9065. [PubMed: 18768700]
- Nan X, Ng HH, et al. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature.* 1998; 393(6683):386–389. [PubMed: 9620804]
- Ng HH, Jeppesen P, et al. Active repression of methylated genes by the chromosomal protein MBD1. *Mol Cell Biol.* 2000; 20(4):1394–1406. [PubMed: 10648624]
- Ng HH, Zhang Y, et al. MBD2 is a transcriptional repressor belonging to the MeCP1 histone deacetylase complex. *Nat Genet.* 1999; 23(1):58–61. [PubMed: 10471499]
- O'Keefe JA, Li Y, et al. Estrogen receptor mRNA alterations in the developing rat hippocampus. *Brain Res Mol Brain Res.* 1995; 30(1):115–124. [PubMed: 7609632]
- O'Keefe JA, Pedersen EB, et al. The ontogeny of estrogen receptors in heterochronic hippocampal and neocortical transplants demonstrates an intrinsic developmental program. *Brain Res Dev Brain Res.* 1993; 75(1):105–112.
- Osterlund MK, Grandien K, et al. The human brain has distinct regional expression patterns of estrogen receptor α mRNA isoforms derived from alternative promoters. *J Neurochem.* 2000; 75(4):1390–1397. [PubMed: 10987818]
- Osterlund MK, Gustafsson JA, et al. Estrogen receptor β (ER β) messenger ribonucleic acid (mRNA) expression within the human forebrain: distinct distribution pattern to ER α mRNA. *J Clin Endocrinol Metab.* 2000; 85(10):3840–3846. [PubMed: 11061547]
- Pfaff D, Keiner M. Atlas of estradiol-concentrating cells in the central nervous system of the female rat. *J Comp Neurol.* 1973; 151(2):121–158. [PubMed: 4744471]

- Prewitt AKWME. Changes in estrogen receptor- α mRNA in the mouse cortex during development. *Brain Res.* 2007; 1134:62–69. [PubMed: 17207781]
- Prins GS, Birch L, et al. Developmental estrogen exposures predispose to prostate carcinogenesis with aging. *Reprod Toxicol.* 2007; 23(3):374–382. [PubMed: 17123779]
- Rhees RW, Shryne JE, et al. Onset of the hormone-sensitive perinatal period for sexual differentiation of the sexually dimorphic nucleus of the preoptic area in female rats. *J Neurobiol.* 1990; 21(5): 781–786. [PubMed: 2394991]
- Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J Steroid Biochem Mol Biol.* 2011; 127(1–2):27–34. [PubMed: 21605673]
- Rubin BS, Murray MK, et al. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect.* 2001; 109(7):675–680. [PubMed: 11485865]
- Sheridan PJ. Estrogen binding in the neonatal neocortex. *Brain Res.* 1979; 178(1):201–206. [PubMed: 91415]
- Shughrue PJ, Lane MV, et al. Comparative distribution of estrogen receptor- α and - β mRNA in the rat central nervous system. *J Comp Neurol.* 1997; 388(4):507–525. [PubMed: 9388012]
- Shughrue PJ, Stumpf WE, et al. Developmental changes in estrogen receptors in mouse cerebral cortex between birth and postweaning: studied by autoradiography with 11 beta-methoxy-16 alpha-[125I]iodoestradiol. *Endocrinology.* 1990; 126(2):1112–1124. [PubMed: 2298154]
- Siegmund KD, Connor CM, et al. DNA Methylation in the Human Cerebral Cortex Is Dynamically Regulated throughout the Life Span and Involves Differentiated Neurons. *PLoS ONE.* 2007; 2(9):e895. [PubMed: 17878930]
- Simerly RB, Chang C, et al. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. *J Comp Neurol.* 1990; 294(1):76–95. [PubMed: 2324335]
- Simpkins JW, Singh M. More than a decade of estrogen neuroprotection. *Alzheimer's and Dementia.* 2008; 4(1, Supplement 1):S131–S136.
- Takizawa T, Meshorer E. Chromatin and nuclear architecture in the nervous system. *Trends Neurosci.* 2008; 31(7):343–352. [PubMed: 18538423]
- Tian YH, Hwan Kim S, et al. Lactational and postnatal exposure to polychlorinated biphenyls induces sex-specific anxiolytic behavior and cognitive deficit in mice offspring. *Synapse.* 2011; 65(10): 1032–1041. [PubMed: 21425352]
- Toran-Allerand CD. Sex steroids and the development of the newborn mouse hypothalamus and preoptic area in vitro: implications for sexual differentiation. *Brain Res.* 1976; 106(2):407–412. [PubMed: 1276881]
- Toran-Allerand CD, Miranda RC, et al. Cellular variations in estrogen receptor mRNA translation in the developing brain: evidence from combined [125I]estrogen autoradiography and non-isotopic in situ hybridization histochemistry. *Brain Res.* 1992; 576(1):25–41. [PubMed: 1515911]
- Vandenberg LN, Maffini MV, et al. Perinatal exposure to the xenoestrogen bisphenol-A induces mammary intraductal hyperplasias in adult CD-1 mice. *Reprod Toxicol.* 2008; 26(3–4):210–219. [PubMed: 18938238]
- Weaver IC, Cervoni N, et al. Epigenetic programming by maternal behavior. *Nat Neurosci.* 2004; 7(8): 847–854. [PubMed: 15220929]
- Westberry JM, Trout AL, et al. Epigenetic regulation of estrogen receptor α gene expression in the mouse cortex during early postnatal development. *Endocrinology.* 2010; 151(2):731–740. [PubMed: 19966177]
- White R, Lees JA, et al. Structural organization and expression of the mouse estrogen receptor. *Mol Endocrinol.* 1987; 1(10):735–744. [PubMed: 2484714]
- Wolffe AP. Epigenetics. Introduction. *Novartis Found Symp.* 1998; 214:1–5. [PubMed: 9601008]
- Yao T, Itoh K, et al. Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. *Biochem Biophys Res Commun.* 2008; 376(3):563–567. [PubMed: 18804091]
- Zoghbi HY. Postnatal neurodevelopmental disorders: meeting at the synapse? *Science.* 2003; 302(5646):826–830. [PubMed: 14593168]

Highlights

- Neuronal gene expression is developmentally regulated in an intrinsic fashion.
- Estrogen receptor alpha expression is shut down by DNA methylation in the cortex.
- Environmental factors can influence the epigenetic machinery in neonatal rodents.