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Corepressors, nuclear receptors, and epigenetic factors on DNA: a tail of repression

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Abstract

The differential exposure to circulating steroid hormones during brain development can have lasting consequences on brain function and behavior; therefore, the tight control of steroid hormone action within the developing brain is necessary for the expression of appropriate sex-typical behavior patterns later in life. The restricted control of steroid hormone action at the level of the DNA can be accomplished through the recruitment of coregulatory complexes. Nuclear receptor action can either be enhanced by the recruitment of coactivator complexes or suppressed by the formation of corepressor complexes. Alternatively, the regulation of nuclear receptor-mediated gene transcription in the developing brain may involve a dynamic process of coactivator and corepressor function on DNA. It is likely that understanding how different combinations of coregulatory matrixes assembly on DNA will lead to further understanding of heterogeneous responses to nuclear receptor activation. We will discuss how coregulators influence gene transcription and repression, the role of chromatin binding factors in the regulation of gene transcription, and their potential impact on brain development.

I. Introduction

The developing brain is elegantly sensitive to steroid hormone exposure, and the differential exposure to steroid hormones between neonatal males and females produces some lasting sex differences in brain physiology and behavior. Most of what we know about how sex differences are organized during the neonatal period comes from studies examining differences in gonadal steroid hormone exposure. However, differences in gonadal steroid hormone exposure do not account for all sex differences observed in brain and behavior. Recent concepts now extend to how sex chromosomes themselves appear to contribute to the sexual differentiation of the brain independently of gonadal hormones (Carruth et al., 2002; De Vries et al., 2002). Furthermore, environmental or social stimuli during the neonatal period, such as variations in maternal care, can also influence sexually dimorphic behaviors in adulthood (Chamove et al., 1973; Moore and Power, 1992; Parent and Meaney, 2008). Presumably, these environmental pathways alter neurotransmitter signaling and subsequently can influence the activity or availability of transcription factors that impact brain differentiation. As gonadal hormones impact brain differentiation mainly by acting upon nuclear receptors, this review will focus on those proteins that regulate the transcriptional efficacy of nuclear receptors on DNA. It is our goal to suggest that it is the

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activity of nuclear receptors and their associated proteins that ultimately determine the response to hormones or other non-hormonal pathways impacting brain differentiation that are critical in sexually differentiating brain and behavior.

II. Steroid-mediated sexual differentiation of the brain

During the perinatal period, male rats are exposed to two major surges of testosterone: one occurring around embryonic day 18 (Weisz and Ward, 1980), and another a few hours after birth (Rhoda et al., 1984). It is the exposure to these two surges, or pulses, that appear to drive most, but not all, sex differences in brain and behavior. Testosterone causes the defeminization of brain areas that would have developed to control female sexual behavior and the masculinization of brain areas that will develop to control male sexual behavior. Testosterone produces these differences mainly via its metabolites estradiol and dihydrotestosterone. While it has been considered that estradiol was the main metabolite in differentiating male from female brain, a role for androgen receptors also appears to be important (Zuloaga et al., 2008). It is not entirely clear that estrogens and androgens are converging on the same systems in the brain, as there are some data suggesting that different components of behavior are differentially impacted by these hormones. For example, estradiol clearly leads to the defeminization of adult female sexual behavior, while dihydrotestosterone appears to have little effect on this behavior. This is in contrast to a major role for androgens in masculinizing juvenile play behavior, with some potential role for estrogen receptors.

One of the first non-mother directed sexually dimorphic social behaviors to emerge during development is juvenile social play behavior (Vanderschuren et al., 1997), with juvenile male rats engage in social play behavior at a higher frequency than do females (Olioff and Stewart, 1978). While neurotransmitters, social experience and epigenetic factors have all been found to affect the development of juvenile social play behavior (Auger and Olesen, 2009), it is mainly the differential exposure to neonatal testosterone exposure that drives the organization of this behavior. For example, castration of neonatal male rats reduces juvenile social play behavior to female typical levels (Beatty et al., 1981; Meaney and Stewart, 1981). In contrast, treating neonatal female rats with testosterone increases juvenile social play behavior to levels that resemble males (Meaney and Stewart, 1981). While the effects of testosterone on the organization of social play behavior are known to occur through its actions on androgen receptors (Casto et al., 2003), there is some data suggesting that estradiol treatment can also influence the organization of juvenile social play behavior (Olesen et al., 2005). These data illustrate the lasting impact of steroid hormones on the organization of behavior.

III. Nuclear receptor expression

Gonadal hormones influence sexual differentiation of the brain and behavior mostly by binding to intracellular nuclear receptors. To understand the functional role of nuclear receptors, it is important to understand their distribution within the brain. Members of the nuclear receptor family are heterogeneously expressed throughout the rat brain (Pfaff and Keiner, 1973); however, these brain regions are interconnected with each other forming a neural “network” to coordinate changes in behavior (Cottingham and Pfaff, 1986). While the distribution of nuclear receptors in the developing and adult mammalian brain has been well documented, we will focus on nuclear receptors mediating the actions of androgens or estrogens in developing brain.

At present, there are two identified types of intracellular estrogen receptors, estrogen receptor α (ER α) and estrogen receptor β (ER β), in the developing and adult brain. ER expression first appears around mid- to late gestation with varying levels of expression

depending upon sex and brain region (DonCarlos, 1996;DonCarlos and Handa, 1994;MacLusky et al., 1979a;MacLusky et al., 1979b). During brain development, ER α levels are higher in neonatal females than males in a variety of brain regions, including the cortex, hippocampus, medial preoptic area (MPOA), ventromedial hypothalamus (VMH), and bed nucleus of the stria terminalis (BST) (DonCarlos, 1996;DonCarlos and Handa, 1994;Kuhnemann et al., 1994;Kuhnemann et al., 1995). ER β is also expressed around birth in many of the same regions as ER α , including the cerebellum (Jakab et al., 2001), ventral midbrain (Raab et al., 1999), cortex, amygdala, BST, paraventricular nucleus, and VMH (Ikeda et al., 2003;Perez et al., 2003). Prenatal expression of ER β mRNA is found in the hippocampus, hypothalamus and preoptic area (Ivanova and Beyer, 2000;Raab et al., 1999). Interestingly, while one study reports that ER β mRNA levels in the hypothalamus/POA are higher in neonatal males than females (Karolczak and Beyer, 1998), another study finds that ER β protein immunoreactivity is higher in neonatal females compared to males within the VMH (Ikeda et al., 2003). Sex differences in ER expression result partly from sex differences in circulating testosterone and its ability to be aromatized (DonCarlos et al., 1995;Kuhnemann et al., 1994;Kuhnemann et al., 1995;Lauber et al., 1991).

Androgen receptor mRNA has been shown to occur within the MPOA, BST, VMH, arcuate nucleus, amygdala, lateral septum, and hippocampus (McAbee and DonCarlos, 1998;Simerly et al., 1990). The distribution of androgen receptors overlaps with the distribution of estrogen receptors (Simerly et al., 1990). The functional significance of this overlap is not known; however, it does provide a mechanism for one steroid hormone or receptor to modulate the actions of another steroid hormone or receptor. For example, estrogen has been shown to influence androgen receptor expression (McAbee and DonCarlos, 1999), and androgens can influence estrogen receptor (Brown et al., 1994).

IV. Molecular Mechanisms of Coregulatory proteins

In general, activation of nuclear receptors results in release of heat shock proteins and conformational change of the receptor. This conformational change is believed to enhance the ability of the steroid-receptor complex to bind to a response elements on DNA (Jensen et al., 1968;Walters, 1985). Once bound to DNA, the receptor complex interacts with various combinations of co-regulatory proteins to influence a diverse array of cellular processes ranging from genomic transcription (Carson-Jurica et al., 1990;McKenna et al., 1999b), changes in second-messenger systems (Etgen et al., 1999), neurotransmitter synthesis and release (Etgen and Karkanias, 1994;Hull et al., 1999;McCarthy, 1994). These difference can elicit lasting changes in cell function, neurochemical phenotype, or neuroanatomical projections (De Vries and Simerly, 2002). Nuclear receptor function on DNA is critically dependent upon available coregulatory proteins that form within the transcriptional complex, which can either increase gene transcription, called coactivators, or decrease gene transcription, called corepressors (Figure 1).

a. Molecular Mechanisms of coactivators

Early evidence of the interaction of coactivators and nuclear receptors include studies in which the phenomenon of squelching was observed, where the transcription of one activated nuclear receptor was decreased in the presence of another unrelated activated nuclear receptor (Meyer et al., 1989). These initial studies lead to the cloning and characterization of SRC-1 (Steroid Receptor Coactivator-1) (Onate et al., 1995). Since then many coactivators have been discovered, including the rest of the p160 family (McKenna et al., 1999a), CBP (CREB binding protein) (Kwok et al., 1994) and p300 (Chakravarti et al., 1996). Coactivators are thought to function by facilitating access of transcriptional factors to the DNA promoter site (McKenna et al., 1999a). Many coactivators appear to accomplish this through their own intrinsic histone acetylase transferase (HAT) activity or through their

association with complexes having HAT activity. The hyperacetylation of histone tails, by HAT activity, decreases their positive charge which leads to the separation of the histone tails and the negatively charged DNA. This change in chromatin structure allows for the recruitment of additional transcriptional factors and subsequently leads to an increase in transcription (McKenna et al., 1999a; Rosenfeld and Glass, 2001). Coactivator function is not limited to HAT activity, and different coactivators have been found to have diverse functions leading to increases in transcription. For example, coactivators have been found to influence ubiquitination, methylation, ATP-dependent chromatin remodeling activity and mRNA splicing (Lonard and O'malley, 2005). Interestingly, coactivator expression is known to be sexually dimorphic (Auger et al., 2002; Charlier et al., 2002; Duncan and Carruth, 2007; Misiti et al., 1998) and regulated by steroid hormones (Charlier et al., 2006a; Mitev et al., 2003; Murphy and Segal, 1997). Coactivators are also important for the development and expression of adult sexually dimorphic behavior (Apostolakis et al., 2002; Auger et al., 2002; Auger et al., 2000; Charlier et al., 2006b; Molenda et al., 2002; Molenda-Figueira et al., 2006).

b. Molecular Mechanisms of Corepressors

In contrast to the function of nuclear receptor coactivators, which is to increase gene transcription, corepressors are generally thought to suppress or silence gene transcription. While more is known about the molecular mechanisms and functions of coactivators, less is known about the functional role of corepressors. The most widely studied corepressors, NCoR (Nuclear Receptor CoRepressor) and SMRT (Silencing Mediator of Retinoid and Thyroid Receptors), were first discovered and identified through their interaction with thyroid and retinoid hormone receptors (Chen and Evans, 1995; Horlein et al., 1995). NCoR and SMRT are not the only corepressors. For example, Alien (Dressel et al., 1999), PSF (polypyrimidine tract-binding protein-associated splicing factor) (Mathur et al., 2001), Hairless (Potter et al., 2001), REA (repressor of estrogen receptor activity) (Montano et al., 1999), RTA (repressor of tamoxifen transcriptional activation) (Norris et al., 2002) and TGIF (5'TG3' interacting factor) (Sharma and Sun, 2001) have also been characterized as corepressors [for review see (Privalsky, 2004)], but less is known about these molecules. While NCoR and SMRT have been found to be very similar in structure, found within similar transcriptional complexes, and even function in a related manner, there are some notable differences that will be later discussed. NCoR and SMRT both interact with nuclear receptors at the promoter site and form larger corepressor complexes that reduce the basal level of transcription. These corepressors are classically thought to decrease gene transcription through their association with histone deacetylase complexes or HDACs (Tsai and O'Malley, 1994). The relative hypoacetylation restores a positive charge on the histone tails and causes the histones to more closely associate with negatively charged DNA, and subsequently less assessable to transcription factors (McKenna et al., 1999a). Interestingly, corepressors can either repress gene expression through their interactions with nuclear receptors or independently of nuclear receptors via their direct or indirect interactions with methyl binding proteins, such as Kaiso (Yoon et al., 2003b) and MeCP2 (Cukier et al., 2008; Kokura et al., 2001).

Corepressors function with Nuclear Receptors—Corepressors interact with a repressor domain on nuclear receptors that overlaps with the surface area that binds coactivators. Hormone binding to nuclear receptors causes a conformational change that favors the recruitment of coactivators over corepressors [for review see (Aranda and Pascual, 2001; Privalsky, 2004; Xu et al., 1999)]. Modifications of the coregulatory proteins, as well as the nuclear receptors, such as acetylation (Fu et al., 2002) and phosphorylation (Zhou et al., 2001), also can change the interacting affinities of these molecules. This sets up an interesting competition for these sites between coactivators and corepressors (Figure 2),

and results in histone and coregulatory protein modification that can take place in minutes to hours (Privalsky, 2004;Shang et al., 2000). These relatively rapid modifications may contribute to a cyclical patterning of nuclear receptor gene transcription.

NCoR and SMRT have been shown to interact with nuclear receptors other than the thyroid and retinoid hormone receptors. NCoR and/or SMRT act as corepressor molecules for androgen receptors (Cheng et al., 2002;Yoon and Wong, 2006), estrogen receptors (Lavinsky et al., 1998), and progesterone receptors (Liu et al., 2002). It remains to be determined if some corepressors have preferential interactions with certain nuclear receptors. While some corepressors can interact weakly, but directly, with nuclear receptors in the presence of the ligand, this interaction can be much stronger in the presence of the antagonists (Figure 2). This is intriguing as we know little about endogenous antagonists to nuclear receptors, suggesting that little is known about what is driving corepressor interactions with nuclear receptors. It also remains to be fully elucidated the extent at which corepressors interact indirectly with nuclear receptors. Interestingly, data indicate that these corepressors may actually be partially responsible for the antagonist ability of some drugs. For example, tamoxifen acts as an estrogen receptor agonist in NCoR knockout mice cells and re-expressing NCoR within these cells restores the antagonistic ability of tamoxifen (Jepsen et al., 2000). RU-486 acts as a progestin receptor antagonist in cells that express a higher ratio of corepressors to coactivators and can switch to an agonist if the ratio is reversed (Liu et al., 2002). Therapeutically, it is important to understand the relative ratios of coregulatory protein expression within tissues as these ratios can determine if a drug will act as an agonist or antagonist when used in treatment for some forms of cancer, such as tamoxifen (Shang and Brown, 2002). Therefore, it is important to understand the function of corepressors, as well as the ratio of coregulatory protein expression, to better predict how a cell responds to environmental or endogenous signals.

On DNA, NCoR and SMRT recruit many proteins to form a large corepressor complex; some of the most studied and well understood of these proteins are the HDACs. Both NCoR and SMRT have been found to interact directly with many of the HDACs, for example both interact directly with HDAC3 (Li et al., 2000;Wen et al., 2000). Proteins that are recruited to the larger corepressor complex can further refine the function and the stability of the complex. Some of the identified proteins that NCoR and SMRT interacts with are Sin3 (Alland et al., 1997;Heinzel et al., 1997), Ski (Nomura et al., 1999), Sno (Nomura et al., 1999;Shinagawa et al., 2000), IR10 (Yoon et al., 2003a), KAP-1 (Underhill et al., 2000), SHARP (Shi et al., 2001), Sun-CoR (Zamir et al., 1997), and BRG1 and BAF (components of the (SWI-SNF complex) (Underhill et al., 2000). These interacting proteins have been associated with a wide variety of cellular processes, including transcription repression, tumor suppression, blastocyst formation and silencing heterochromatin. Therefore, the functional roles of some corepressors may be diverse.

Corepressors function with methyl-binding proteins—Most research on corepressors has been focused on determining how these corepressors function on nuclear receptors to repress transcription. However, genes may also be repressed via methylation of CpG sites by DNA methyltransferases (DNMTs) (Klose and Bird, 2006). DNA methylation can cause gene inhibition directly by interfering with binding of transcriptional proteins to DNA, but it can also cause gene repression by allowing the binding of methyl-binding proteins. Methyl-binding proteins then recruit corepressor complexes, some of which contain NCoR and SMRT. Therefore, NCoR and SMRT can repress gene expression not only by acting as corepressors of nuclear receptors, but also via their interactions with methyl-binding proteins. NCoR has been found to interact directly with methyl-binding proteins such as Kaiso (Yoon et al., 2003b) and MeCP2 (Cukier et al., 2008;Kokura et al., 2001). Corepressor complexes interacting with methyl-binding proteins cause gene

repression in a similar manner as when corepressors interact with nuclear receptors. That is, they cause the recruitment of HDACs, which deacetylate histones, leading to condensation of the chromatin and gene silencing (Klose and Bird, 2006).

A diverse array of corepressor complexes can form on DNA, following recruitment by methyl-binding proteins, to repress gene transcription. These include Sin3, NuRD, CoREST, and the NCoR/SMRT repressor complexes (Cunliffe, 2008). While the components of these corepressor complexes are still being identified, there are some shared and some unique molecules that form these complexes (Cunliffe, 2008). Both Sin3 and NuRD complexes contain HDAC1, HDAC2, RbAp46, and RbAp48. However, the Sin3 complex contains Sin3a, SAP18, and SAP30; whereas, the NuRD complex contains MBD3, MTA-2, and Mi-2. More variations appear to be found within the CoREST and SMRT/NCoR repressor complexes. The CoREST complex contains HDAC1, HDAC2, CoREST, SHARP and Sin3. The SMRT/NCoR complex contains HDAC3, SMRT, and NCoR. It is likely that these relatively unique multi-protein combinations may have different functional consequences on gene transcription. It is also important to note that while NCoR and SMRT can be found within the same complex, they can also act independent of each other. As the recruitment of corepressor complexes to DNA can occur following interactions with nuclear receptors or methyl-binding proteins, there exists the potential for specification of function by which complexes are formed on DNA. A further diversification can be obtained by having distinct associations of corepressors complexes with methyl-binding proteins. Indeed, MeCP2 associates with the Sin3 corepressor complex, whereas, MBD2 is associated with the NuRD complex.

V. Corepressors in Brain and Behavior

As briefly reviewed above, corepressor molecules can influence gene expression via their interactions with nuclear receptors or through their interactions with methyl-binding proteins. It is likely that the differential interactions with nuclear receptors or methyl-binding proteins elicit unique functional outcomes. To help understand the functional role of corepressor proteins, it is important to understand the expression and regulation of these proteins.

a. Corepressor Expression and Regulation

NCoR and SMRT mRNA appear to be ubiquitously present throughout the adult rat brain; however, differences in the expression levels between NCoR and SMRT were observed in some areas including the brain stem, thalamus, hypothalamus and hippocampus (van der Laan et al., 2005). These findings contribute to the idea that differences in coregulatory proteins may contribute to tissue-specific sensitivity to hormones and other stimuli. Subcellular distribution of corepressors is also important for the function of the cell. Differences in NCoR location, cytoplasmic versus nuclear, has been indicated in abnormal function in colorectal cancer cells (Nagy et al., 1997) as well as critical in determining cell fate (Hermanson et al., 2002).

The regulation of these corepressors has been relatively understudied. Early work reported that neither NCoR nor SMRT were influenced by thyroid hormone using in vitro studies on pituitary cell and in vivo studies examining the anterior pituitary. While estradiol treatment had no effect on NCoR levels, it briefly increased SMRT levels in the anterior pituitary, and was followed by a rapid decrease in SMRT levels (Misiti et al., 1998). In a more recent study, estradiol was found to down-regulate NCoR mRNA, but not SMRT levels, in estrogen receptor-positive breast cancer cells (Frasor et al., 2005). This estradiol induced decrease in NCoR levels was hypothesized to have possible global effects as the transcription levels of other genes regulated by NCoR could possibly be affected. Thyroid

hormone may also influence the expression of corepressors, but it appears that this influence is region dependent (Iannacone et al., 2002; Martinez de et al., 2000). Growth factors, through a MAPK cascade, have also been shown to regulate SMRT function leading to inhibition of the ability of SMRT to interact with other transcriptional factors and increases the cytoplasmic localization of SMRT; however, NCoR does not seem to be affected by this particular pathway, but may be affected by other growth factors and cytokines (Jonas and Privalsky, 2004).

b) Corepressors and Brain Development

NCoR appears to be a required component for gene repression during early development as deletion of the NCoR gene is embryonic lethal. It is interesting to note that SMRT, or another corepressor, is not able to compensate for the loss of NCoR during this developmental period. Cells derived from NCoR knockout mice show altered patterns of transcription affecting development of the brain, indicating that NCoR may be involved in neural stem cell differentiation (Hermanson et al., 2002; Jepsen et al., 2007). For example, the phosphorylation of NCoR by Akt leads to the reversal of repression by NCoR and its localization to the cytoplasm, and appears to be critical in mediating neural stem cell differentiation; this phosphorylation pathway does not seem to have an effect on SMRT (Hermanson et al., 2002). However, SMRT also plays a critical role in brain development and in maintenance of neural stem cell fate. Specifically, SMRT has been found to repress the ability of an unliganded retinoic acid receptor to initiate neural differentiation (Jepsen et al., 2007). NCoR appears to interact with another corepressor, CoREST, to regulate neuronal differentiation. Interestingly, not only the presence of coregulators found within a complex during neuronal differentiation can regulate gene expression, but also the dynamic redistribution of these proteins on or off DNA can further modify the levels of expression. For example, the presence of REST, CoREST, NCoR, mSin3, MeCP2, and HDACs within a complex can regulate gene expression, but how these proteins interact with each other or on DNA can further determine the levels of gene expression (Ballas et al., 2005). This indicates that repressors not only suppress gene transcription but also participate in the fine tuning of expression levels.

c) Corepressors and Behavior

A clear role for corepressors in regulating behavior remains to be fully elucidated. While the use of knockouts have been useful for investigating the functionality of coactivators in modifying behavior, there are fewer models to examine the functional role of corepressors in the brain. Interestingly, the most widely studied corepressor knockout, NCoR, is embryonically lethal. As corepressors interfere with steroid hormone action, it is likely to be involved in processes that are sensitive to steroid hormones. Indeed, hormone resistance syndromes, correlate with mutations that affect the ligand binding domain of thyroid hormone receptor beta that enhances ligand-independent interaction with NCoR/SMRT (Yoh et al., 1997). Due to its relationship with methyl-binding proteins, it is also likely to play a role in modulating epigenetic processes which may influence behavior. For example, as maternal care can influence the organization of sexual dimorphic behaviors (Cameron et al., 2008; Chamove et al., 1973; Parent and Meaney, 2008), and variations in maternal care alters DNA methylation patterns (Champagne et al., 2006), it is possible that these epigenetic processes contribute to the differentiation of juvenile social play behavior. Indeed, we have recently reported that disruption of one methyl-binding protein, MeCP2, disrupts the organization of juvenile social play behavior (Kurian et al., 2008). Specifically, local disruption of MeCP2 expression within the developing amygdala interfered with the organization of juvenile social play behavior in males only. As testosterone action in the developing amygdala is critical for normal organization of male juvenile social play, it is possible that reducing MeCP2 expression interfered with testosterone-induced

masculinization of play. Recently, MeCP2 has been suggested to participate in the dynamic activity of estrogen receptor mediated gene transcription on DNA, and that disruption of estrogen receptor cycling on and off DNA may interfere with overall gene transcription (Metivier et al., 2008). This suggests that interfering with molecules that participate in nuclear receptor cycling on DNA may interfere with steroid hormone action in developing brain.

Disruption in normal functioning of methyl-binding proteins is also implicated in some human disorders; therefore, it is possible that abnormal functioning of corepressors might impact some of these epigenetically related neural developmental disorders. Mutations in the X-linked MECP2 gene, leading to disruption in MeCP2 protein function, are thought to be the direct cause of Rett syndrome, a progressive neurodevelopmental disorder (Amir et al., 1999). Recently, MeCP2 has been shown to directly interact with Sin3a, Rest, as well as NCoR, and it has been suggested that these proteins may be better therapeutic targets than MeCP2 (Cukier et al., 2008). MeCP2 has also been reported to interact with the SMRT corepressor complex. Interestingly, the truncated form of MeCP2, which occurs in Rett syndrome, does not interact with the SMRT complex in developing neurons (Stancheva et al., 2003). The failure of MeCP2's interaction with SMRT is suggested to cause abnormal neuronal differentiation. Furthermore, abnormal subcellular distribution NCoR is found in humans with Huntington's disease and in the mouse model of Huntington's disease (Boutell et al., 1999). These suggest that abnormal corepressor function is implicated in abnormal neuronal function; therefore it is possible that abnormal NCoR function might result in atypical behavior. Indeed, we have found that reducing NCoR expressing during brain development appears to have lasting consequences on juvenile behavior in rats (unpublished data).

VI. Summary

As nuclear receptors are involved in numerous processes within an organism, it is crucial to understand how coregulatory proteins govern nuclear receptor activity. The modification of coregulatory proteins may be an additional mechanism for how relatively few molecules can impact a large number of transcriptional responses and refine how these molecules respond to diverse environmental signals. Differences in coregulatory protein expression or modification may partly explain why some individuals respond differently to steroid hormone exposure or may allow for individuals to compensate for differences in hormone exposure, receptors levels, or coregulatory expression. The functional role for corepressors on behavior has yet to be fully determined. An interesting challenge is that corepressors can function to repress gene transcription through their interactions with nuclear receptors or methyl-binding proteins, and sometimes these proteins regulate the same behavior. Indeed, both nuclear receptors and methyl-binding proteins influence the development of sexually dimorphic behaviors, such as juvenile social play behavior (Casto et al., 2003; Kurian et al., 2008). Therefore, it is reasonable to suspect that corepressors may influence the organization or expression of behavior that is modified by nuclear receptors or methyl-binding proteins. It will be important to determine the role of corepressors as well the mechanisms of how corepressors regulate brain and behavior.

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Figure 1. Simplified models of coregulatory matrixes. Top model illustrates agonist bound nuclear receptors associated with coactivators and additional proteins leading to increased gene transcription. Coactivators can increase gene transcription via the acetylation of histones and through the recruitment and stabilization of the transcriptional complex. Bottom model illustrates antagonist bound nuclear receptors associated with corepressors and additional proteins leading to decreased gene transcription. Corepressors repress gene expression by causing the deacetylation of histones via the recruitment of HDACs to the genome. HRE, hormone response element; NR, nuclear receptor; SRCs, p160 steroid receptor coactivator family; CBP, CREB-binding protein; P/CAF, p300/CBP-associated factor; MED, mediator complex; HDACs, histone deacetylases; Ac, acetyl groups; Pol II, RNA Polymerase II; TBP, TATA-binding protein; TAFs, TBP-associated factors; TATA, TATA box.

Figure 2.

Simplified model of corepressor interactions with nuclear receptors. Top model illustrates theoretical model of nuclear corepressors interacting with antagonist bound nuclear receptors leading to gene repression. Middle model illustrates coregulatory proteins competing for binding sites on nuclear receptors to modulate receptor activity. Bottom panel illustrates corepressor binding to unliganded (Apo) nuclear receptors (i.e., Apo-ER) to repress activity.