Published in final edited form as:
J Neuroendocrinol. 2009 March ; 21(4): 229–237. doi:10.1111/j.1365-2826.2009.01827.x.

Nuclear receptor coactivators: Essential players in steroid hormone action in brain and behavior

Marc J. Tetel
Neuroscience Program, Wellesley College, 106 Central St., Wellesley, MA 02481

Abstract

Steroid hormones act in brain and throughout the body to influence behavior and physiology. Many of these effects of steroid hormones are elicited by transcriptional events mediated by their respective receptors. A variety of cell culture studies reveal that nuclear receptor coactivators are critical in modulating steroid receptor-dependent transcription. Thus, in addition to the availability of the hormone and the expression of its receptor, nuclear receptor coactivators are essential for steroid-dependent transactivation of genes. This review will discuss the mounting evidence that nuclear receptor coactivators are critical in modulating steroid hormone action in brain and the regulation of behavior.

Keywords

steroid receptor coactivator-1 (SRC-1); estrogen receptor; progestin receptor; brain development; sex behavior

Introduction

Steroid hormones have profound effects on homeostasis, development, reproduction and behavior. Many of the biological effects of steroid hormones are mediated through their respective receptors, which are members of the steroid/nuclear receptor superfamily of transcriptional activators (1,2). Receptors for estrogens (ER) and progestins (PR) can function in a classic, genomic mechanism by acting as ligand-dependent nuclear transcription factors. Nuclear receptor coregulators, consisting of coactivators and corepressors, are critical in modulating the transcriptional activity of ER and PR, as well as other nuclear receptors. While ER and PR can also function in brain independent of ligand and at the membrane to rapidly activate cytoplasmic signaling pathways (3–6), these receptors elicit many changes in behavior and physiology by acting through classic, genomic mechanisms. This review will focus on the function of these important nuclear receptor coactivators in genomic mechanisms of ER and PR action in brain and behavior.

Steroid receptor structure and genomic mechanisms of action

Steroid receptors have a modular domain structure consisting of an amino-terminal region (N-domain), a central DNA binding domain (DBD) and a carboxy-terminal ligand binding domain (LBD) (1,2). In general, steroid receptors have two transcriptional activation domains: one in the amino terminal (AF-1) and one in the carboxyl terminal LBD (AF-2) (7). Intracellular ER exist in two forms, α and β, which are transcribed from different genes (8,9). These subtypes differ in their abilities to bind different ligands (10), distribution in

Correspondence should be addressed to Marc J. Tetel: Phone: 781-283-3003, Fax: 781-283-3642, mtetel@wellesley.edu.

brain (11–14), and functions in brain and behavior (15–18). In addition, cell culture experiments indicate that ERα is a stronger transcriptional activator than ERβ, due to differences in the AF-1 region (19). In most species, PR are expressed in two forms; the full-length PR-B and the truncated PR-A, which are encoded by the same gene but are under the regulation of different promoters (20). Under certain conditions, *in vitro* studies indicate that human PR-B is a stronger transcriptional activator than PR-A (21–23), due to an additional AF domain in the N-terminus of PR-B (24). These two PR isoforms appear to have distinct functions in reproductive behavior and physiology (25,26).

In the classic, ligand-dependent, genomic mechanism of action of steroid receptors, in the absence of hormone, receptors are complexed with several chaperone molecules, including heat shock proteins (hsp). These interactions are requisite for proper protein folding and assembly of stable receptor-hsp heterocomplexes that are competent to bind ligand (27). Upon binding hormone, steroid receptors undergo a conformational change that causes dissociation of these hsp and allow receptors to dimerize (28). Activated receptors bind directly to specific steroid response elements (SREs) and SRE-like sequences in the promoter regions of target genes (1,2). Binding of receptors to DNA increases or decreases gene transcription by altering the rate of recruitment of general transcription factors and influencing the recruitment of RNA polymerase II to the initiation site (29,30). Thus, in brain it is thought that steroids can act via their respective receptors to alter neuronal gene transcription, resulting in profound changes in behavior and physiology (31,32).

Nuclear Receptor Coregulators

Nuclear receptor coregulators are required for efficient transcriptional regulation by nuclear receptors (33,34). The importance of these coregulators in a variety of human diseases, including cancer and some neurological disorders, is becoming more apparent (35). Coregulators consist of coactivators and corepressors that are required for efficient transcriptional regulation by nuclear receptors. Nuclear receptor coactivators dramatically enhance the transcriptional activity of nuclear receptors, including ER and PR (33,34). Nuclear receptor coactivators influence receptor transcription through a variety of mechanisms, including acetylation, methylation, phosphorylation and chromatin remodeling (33). *In vitro* studies using antibodies against nuclear receptor coactivators indicate that recruitment of coactivators is rate-limiting in steroid receptor-mediated gene transcription (33,36). In further support for nuclear receptor coactivator-dependent facilitation of transcription *in vitro*, squelching, or the repression of the transcriptional activity of one steroid receptor by another, is reversed by the addition of coactivators (37). Thus, a critical component of efficient steroid receptor transcription is the recruitment of nuclear receptor coactivators, which dramatically enhance transcriptional activity. Under most conditions, steroid receptors interact with coactivators in the presence of an agonist, but not in the absence of ligand or in the presence of an antagonist or a selective receptor modulator (37–40) but *c.f.* (41–43). Corepressors and their complexes associate with nuclear receptors when unliganded or bound to antagonists and serve to repress nuclear receptor transcription by recruiting corepressor complexes to the cis-active elements in the promoter and enhancers of target genes (33).

Coactivators of steroid receptors

The p160 family

Steroid receptor coactivator-1 (SRC-1/NcoA-1) was one of the first coactivators found to interact with hormone-bound steroid receptors (37). SRC-1 is a member of a larger family of p160 proteins that includes SRC-2 (also known as GRIP1, TIF2 and NCoA-2) (44,45) and SRC-3 (AIB1, TRAM-1, p/CIP, ACTR, RAC3) (46,47). The SRC family of coactivators

physically interacts with steroid receptors, including ER and PR, in a ligand-dependent manner (33,34,37). The SRCs physically associate with agonist-bound receptors through multiple LXXLL motifs (L, leucine; X, any amino acid) that make up nuclear receptor (NR) boxes (48). *In vitro* experiments reveal that depletion of SRC-1 in cultured cells by micro-injection of antibodies to SRC-1 prevents receptor-dependent transcription, suggesting that SRC-1 is important for transcriptional activity of steroid receptors (36). In cell culture, hormone induced transactivation of PR is reduced by coexpression of ERα, presumably due to squelching or sequestering of shared coactivators (37). This squelching can be reversed by over-expression of SRC-1, suggesting that coactivators are a limiting factor necessary for full transcriptional activation of receptors (37). In further support, over-expression of SRC-1 relieves thyroid hormone receptor inhibition of ERα-mediated transcription in a neuroendocrine model (49).

The SRC family of coactivators appear to act as a platform for the recruitment of other coactivators, including CREB binding protein (CBP) and p300/CBP associated factor (p/CAF), that possess histone acetyltransferase activity and aid in chromatin remodeling (50,51). The p160 coactivators contain two activation domains, AD1 and AD2, in the C-terminal region. AD1 mediates interactions with CBP (52), while AD2 allows binding of other proteins, including the protein arginine methyltransferase CARM1 (53).

Studies with knock-out mice have revealed much about the *in vivo* function of these coactivators. SRC-1 knockout mice, while fertile, have decreased responsiveness in progesterone target tissues (54), partial resistance to thyroid hormone (55) and delayed development of cerebellar Purkinje cells (56). In addition, SRC-1 is critical in maintaining energy balance by regulating both energy intake and expenditure (57).

As is the case with SRC-1, SRC-2 enhances transcriptional activity of a variety of nuclear receptors, including ER and PR (44,45). The mid-region of the SRC-2 protein, which mediates interactions with steroid receptors, has relatively low homology with SRC-1, suggesting functional differences between these two proteins (44,45). SRC-2 KO mice reveal that this coactivator is important in fertility and ductal branching in mammary gland (58–60). Microarray analysis of uteri from SRC-2 null mice reveal that SRC-2 is involved in the ability of progesterone to repress specific genes involved in a variety of functions, including cell cycle and immunity (61).

SRC-3/AIB1, which is amplified in human breast tumors (46), coactivates a variety of nuclear receptors, including ER and PR (36,46,62). Female SRC-3 null mice, while fertile, have delayed puberty, longer estrous cycles, ovulate fewer eggs and have impaired mammary gland development (63,64). Using chromatin immunoprecipitation (ChIP) assays, GnRH stimulated more efficient recruitment of SRC-3 by PR, on the PRE of a luciferase reporter gene of the gonadotropin α subunit gene promoter, than progesterone (65). These findings suggest that phosphorylation of PR and its interaction with SRC-3 and binding to DNA may play an important role in the possible ligand-independent activation of PR by GnRHs (65).

Other coactivators of steroid receptors

While CREB binding protein (CBP) was initially discovered to be a transcriptional activator of cAMP-response element binding protein (CREB) (66,67), it is also now known to function as an integrator of nuclear receptors with other cell signaling pathways, including CREB and AP-1 (51,67,68). As is the case with the p160 family, CBP is important in ligand-dependent transcriptional activity of nuclear receptors, including ER and PR (69). Interestingly, mutation of the CBP gene causes Rubinstein-Taybi syndrome, which results in severe mental retardation and a variety of physiological deformities in humans (70). In mice,

mutations of CBP lead to similar physical deformities as well as impaired memory (71). A variety of *in vitro* studies indicate that SRC-1 and CBP act synergistically to enhance ER and PR transcriptional activity and function (69,72–74). In support of this concept, SRC-1 physically interacts with CBP and recruits it to the coactivator complex to form a ternary complex at target gene promoters (51,69).

Steroid receptor RNA activator (SRA) is a unique coactivator in that it functions as an RNA transcript to enhance transcriptional activity of steroid receptors, including PR, ER, GR and AR (75,76). While liganded ER reduced PR transcriptional activation, addition of SRA reversed this squelching effect of ER (76). Treatment of cells with antisense to both SRC-1 and SRA greatly reduced activity of ERα or PR (75,76). Antisense to either SRA or SRC-1 alone had a less dramatic effect on ERα activity, suggesting SRA association with SRC-1 (75). In further support, SRA copurified with SRC-1, indicating that SRA exists in a ribonucleoprotein complex containing SRC-1 (76). Expression of SRA is tissue specific, with SRA mRNA expressed at high levels in liver, skeletal muscle and heart, and at lower levels in brain and placenta (76). Over-expression of SRA in transgenic mice reveals a role for SRA in estrogen-induced expression of PR in mammary gland (77).

Finally, there are a variety of other coactivators, including ERAP140 (78), TRAP220 (79), PGC-1 (80), chromatin high mobility group proteins 1 and 2 (81) and TIP60 (82), that are known to interact with ER and PR. With over 285 coactivators and corepressors identified to date (83), there is much more to be learned about the function of coregulators in nuclear receptor action.

Function of nuclear receptor coactivators in brain and behavior

While much is known about the molecular mechanisms of nuclear receptor coactivators from a variety of cell culture studies (33,34), we are just beginning to understand their role in hormone action in brain. SRC-1 mRNA and protein are expressed at high levels in the cortex, hypothalamus and hippocampus, and low levels in the lateral septum, of rodents (84–90) and birds (91). In order for coactivators to function with steroid receptors, they must be expressed in the same cells. Indeed, SRC-1 is expressed in the majority of estrogen-induced PR cells in reproductively-relevant brain regions, including the VMN, medial preoptic area and arcuate nucleus (92). Given that virtually all estradiol-induced PR cells in the hypothalamus contain ERα (93,94), these findings suggest that these specialized cells represent functional sites of interaction between ovarian steroid receptors and SRC-1 in brain (92). It is important to note that not all SRC-1 immunoreactive cells expressed PR, suggesting that SRC-1 may function with other nuclear receptors in these cells (92). The expression of the SRC family of coactivators in brain appears to be regulated by a variety of factors, including hormones (95–101), daylength (102) and stress (97,103,104).

The function of nuclear receptor coactivators in hormone action in brain and behavior has been investigated. In collaboration with Tony Auger and Peg McCarthy, we investigated the role of SRC-1 in hormone-dependent sexual differentiation of the rodent sexually dimorphic nucleus (SDN) of the POA (88). On postnatal days (PN) 0–2, the hypothalami of female rat pups were bilaterally infused with antisense oligonucleotides (ODNs) to SRC-1 mRNA or scrambled control ODNs. On PN1, female pups were treated with the aromatizable androgen, testosterone propionate, to increase SDN volume. At PN13, antisense to SRC-1 was found to reduce the volume of the SDN of androgenized females by 46% compared to females receiving control ODNs. The testosterone surge in males just after birth suppresses the development of female sexual behavior in adulthood (105,106). This suppression is due to estradiol, aromatized from testosterone, binding to ER (107). To test if SRC-1 was critical in development of sexual behavior, androgenized female and male rats were treated with

SRC-1 antisense or control ODNs on PN0-2 (88). Males were castrated in adulthood and following testosterone treatment, were tested for male and female sex behavior. Males and androgenized females treated with SRC-1 antisense displayed higher levels of female sexual behavior than did rats treated with control ODNs. Taken together, these findings suggest that reduction of SRC-1 in brain decreases ER activity, and thus alters brain development and inhibits the defeminizing actions of estrogen during development (88).

CBP is expressed in reproductively-relevant brain areas in a dimorphic manner, and functions in the development of masculine sexual behavior (108). On the day of birth, males express 53% more CBP-immunoreactive (CBP-IR) cells in the mPOA, while females express 83% more CBP-IR cells in the VMN than males. These findings of differential expression of CBP suggest that gonadal steroid hormones alter levels of CBP in the brain during development, which in turn influence neural steroid responsiveness. In this same study, testosterone-treated females that received CBP antisense in the hypothalamus on PN0-2 displayed higher levels of lordosis than androgenized females treated with control ODNs (108). Taken together with the previous study, it appears that both SRC-1 and CBP are necessary for ER action in the developing brain.

Our lab and others have investigated the role of nuclear receptor coactivators in hormone-dependent gene expression in brain and behavior in adult rodents (89,109). Estradiol-induction of PR gene expression in the VMN is important for hormone-dependent female sexual behavior (110). Therefore, we tested the hypothesis that SRC-1 and CBP are critical in modulating ER-mediated transactivation of the PR gene in the VMN. Infusions of antisense ODNs to SRC-1 and CBP mRNA into one side of the VMN of adult female rats reduced the expression of ER-mediated activation of PR gene expression compared to the contralateral control ODN-treated VMN (89). These findings are supported by previous *in vitro* studies indicating that SRC-1 and CBP function together to modulate ER activity (69). In further support of SRC-1 and CBP/p300 functioning together in brain, neurons in the rat hippocampus and dentate gyrus coexpress SRC-1 and p300 (90). A similar study in brain supports these findings and extend them to include a role of SRC-2, but not SRC-3, in ER-mediated induction of PR in the VMN (109). Finally, the p160 coactivators function in glucocorticoid receptor (GR) action in glial cells (111) and in GR-mediated repression of the corticotropin-releasing hormone gene (112). Taken together, these findings indicate that nuclear receptor coactivator action in brain is essential for full steroid receptor transcriptional activity.

Given that nuclear receptor coactivators are critical for hormone-dependent gene expression in brain, we tested the hypothesis that these coactivators act in brain to modulate the expression of hormone-dependent behaviors (89). Female rats treated with antisense to both SRC-1 and CBP mRNA into the VMN displayed reduced levels of hormone-dependent female sexual receptivity compared to scrambled treated controls (89). Another study supported these findings with SRC-1 and extended them to include a role for SRC-2 in hormone-dependent behavior (109). Our lab has gone on to isolate the effects of these nuclear receptor coactivators on both ER- and PR-dependent aspects of female sexual behavior. There are two modes of hormone regulated female reproductive behavior in rats: estrogen-mediated (elicited by estradiol alone) and progesterone-facilitated (requires estradiol priming followed by progesterone) (32). To test the hypothesis that nuclear receptor coactivators function in brain to modulate ER-mediated aspects of female reproductive behavior, animals were injected with estradiol only (113). Antisense to SRC-1 and CBP infused into the VMN of animals treated with estradiol alone decreased lordosis intensity and frequency, suggesting that these coactivators modulate ER-mediated aspects of female sexual behavior. Proceptive behaviors by the female, which serve to solicit interaction by the male, are PR-dependent and include ear-wiggling and hopping and darting

(114–119). Infusion of antisense to SRC-1 and CBP mRNA into the VMN around the time of progesterone administration reduced PR-dependent ear wiggling and hopping and darting, but did not alter lordosis (113). Thus, it appears that nuclear receptor coactivators function in brain to modulate PR and ER action and influence specific aspects of hormone-dependent sexual behaviors in rodents. Interestingly, while SRC-1 and SRC-2 are expressed at high levels in the hypothalamus, SRC-3 is not (101,109). However, SRC-3 is expressed at high concentrations in the hippocampus (109). In future studies it will be important to distinguish the functions of these different coactivators in hormone action in brain.

Recently, we have begun to take a proteomics-based approach to study the interactions of steroid receptors with coactivators from rat brain. To test the hypotheses that SRC-1 from brain physically associates with ER and PR subtypes in a ligand-dependent manner, pull-down assays with brain tissue from female rats were developed (120). SRC-1 from hypothalamus or hippocampus interacted with ERα and ERβ when bound to estradiol (Figure 1A), which was confirmed by mass spectrometry (120). SRC-1 may function with ERα in the hypothalamus to mediate expression of female sexual behavior (15–17,121), and with both ER subtypes in the hippocampus to differentially modulate estrogen's effects on cognition (18,122) and stress (18,123). Very little to no association of SRC-1 from brain was detected with ERα or ERβ in the absence of ligand or in the presence of the selective ER modulator (SERM) tamoxifen. These findings suggest tamoxifen is functioning as an antagonist to prevent receptor-coactivator interactions, and are consistent with a variety of studies using cell lines demonstrating that estradiol facilitates, while antagonists prevent, SRC-1 association with ER (124–126). In contrast to our findings using brain tissue, cell culture studies suggest that both ERα and ERβ can recruit coactivators to AF-1 in the absence of ligand under certain phosphorylation conditions (127,128). While little to no interactions between receptor and SRC-1 from brain in the absence of ligand were detected, it will be important to investigate whether physiologically-relevant events that modulate ligand-independent activation impact on receptor-coactivator interactions in brain.

In our studies, SRC-1 from the hippocampus appears to interact equally with ERα and ERβ (Figure 1B). In contrast, SRC-1 obtained from hypothalamic extracts interacted more with ERα than with ERβ (Figure 1B). The different functions of the ER subtypes in brain (discussed above) may be explained in part by the lower transcriptional activity of ERβ observed in particular cell lines (19). These differences in transcriptional abilities between ERα and ERβ may be attributed to differential recruitment of coactivators, or differences in the ability of the same coactivator to facilitate transcription of the ER subtypes (129). While some studies using recombinant SRC-1 (129) are consistent with our findings that SRC-1 from brain interacts more with ERα than with ERβ, other studies suggest that SRC-1 associates equally with each ER subtype (130, 131). While these later findings are consistent with our results using SRC-1 from hippocampus, we observed that SRC-1 from hypothalamus interacted more with ERα than with ERβ. These data suggest that ERα is a more efficient transcriptional activator of SRC-1 dependent signaling pathways in the hypothalamus than ERβ. In support, previous findings from our lab indicate that SRC-1 function in the hypothalamus is important for maximal expression of ER-mediated female sexual behavior (113), which appears to be ERα-dependent (15, 132). In addition, SRC-1 from brain interacts more with PR-B than with PR-A (120). These differential interactions of SRC-1 from hypothalamus or hippocampus with the ER and PR subtypes suggest that these brain regions have distinct expression patterns of cofactors involved in these important protein-protein interactions. In addition, it is possible that SRC-1 undergoes differential phosphorylation in these two brain regions, leading to distinct patterns of interaction with receptors. Future experiments will need to apply mass spectrometry analysis to determine if, in a brain region specific manner, different cofactors are present in the receptor-coactivator complex and/or if SRC-1 undergoes differential phosphorylation. Finally, these findings

suggest the importance of using biologically-relevant tissue, in contrast to the use of cell lines alone, in investigating receptor-coactivator interactions. It may be that other cofactors and proteins that are present in tissue (*e.g.* brain) are important for appropriate SRC-1 interactions with receptor. Understanding how nuclear receptor coactivators function with various steroid receptors, and their subtypes, is critical to understanding how hormones act in different brain regions to profoundly influence physiology and behavior. Ultimately, investigation of these receptor-coactivator interactions using brain tissue may allow the identification of novel cofactors involved in the steroid receptor complex in brain.

The function of coregulators has also been studied in hormone action in bird brain. SRC-1, CBP and L7-SPA are expressed at high levels in steroid-sensitive brain regions of adult quail (91), European starlings (133) and zebra finches (134), respectively. In adult quail, infusion of antisense to SRC-1 mRNA reduced testosterone-dependent male copulatory behaviors (135). In addition, SRC-1 was found to function in testosterone-dependent sex differences in brain volume and aromatase expression in the preoptic medial nucleus of the quail (135,136). These findings indicate that SRC-1 is important in the modulation of hormone-dependent gene expression, brain plasticity and behavior in birds.

Summary

The mechanisms by which steroids act in a region-specific, and cell type-specific, manner is a fundamental issue in steroid hormone action in brain. Recent investigations indicate that, in addition to the bioavailability of hormone and receptor levels, nuclear receptor coactivators are critical molecules in modulating steroid receptor-mediated transcription. Studies from cell lines have revealed much about the molecular mechanisms of action of these coactivators. Furthermore, work in brain, as well as other steroid-sensitive tissues, indicates that nuclear receptor coactivators are critical in the fine-tuning of steroid-responsiveness within individual cells. Understanding the recruitment of different coactivator and corepressor complexes to the promoter, which is likely to be cell and tissue specific, will be critical to understanding how hormones function in the brain to regulate complex behaviors.

Acknowledgments

Studies contributed by the author's laboratory were supported by grants from National Science Foundation IBN 0080818 and National Institutes of Health R01 DK61935.

References

1. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. The nuclear receptor superfamily: the second decade. Cell. 1995; 83:835–839. [PubMed: 8521507]
2. Tsai MJ, O'Malley BW. Molecular mechanisms of action of steroid/thyroid receptor superfamily members. Annual Review of Biochemistry. 1994; 63:451–486.
3. Mani S. Mini Review: Progestin Receptor Subtypes in the Brain: The known and the Unknown. Endocrinology. 2008
4. Micevych PE, Mermelstein PG. Membrane estrogen receptors acting through metabotropic glutamate receptors: An emerging mechanism of estrogen action in brain. Molecular Neurobiology. 2008; 38(1):66–77. [PubMed: 18670908]
5. Kelly MJ, Ronnekleiv OK. Membrane-initiated estrogen signaling in hypothalamic neurons. Mol Cell Endocrinol. 2008; 290(1–2):14–23. [PubMed: 18538919]
6. Vasudevan N, Pfaff DW. Non-genomic actions of estrogens and their interaction with genomic actions in the brain. Frontiers in Neuroendocrinology. 2008; 29(2):238–257. [PubMed: 18083219]

7. Tora L, White J, Brou C, Tasset D, Webster N, Scheer E, Chambon P. The human estrogen receptor has two independent non-acidic transcriptional activation functions. Cell. 1989; 59:477–487. [PubMed: 2805068]
8. Jensen EV, Suzuki T, Kawasima T, Stumpf WE, Jungblut PW, de Sombre ER. A two-step mechanism for the interaction of estradiol with rat uterus. Proceedings of the National Academy of Sciences USA. 1968; 59:632–638.
9. Kuiper GGJM, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson J. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. Proceedings of the National Academy of Sciences USA. 1996; 93:5925–5930.
10. Kuiper GGJM, Carlsson B, Grandien K, Enmark E, Häggblad J, Nilsson S, Gustafsson J. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 1997; 138:863–870. [PubMed: 9048584]
11. Shughrue PJ, Lane MV, Merchenthaler I. Comparative distribution of estrogen receptor-alpha and-beta mRNA in the rat central nervous system. J Comp Neurol. 1997; 388(4):507–525. [PubMed: 9388012]
12. Greco B, Allegretto EA, Tetel MJ, Blaustein JD. Coexpression of ER beta with ER alpha and progestin receptor proteins in the female rat forebrain: Effects of estradiol treatment. Endocrinology. 2001; 142:5172–5181. [PubMed: 11713212]
13. Osterlund M, Kuiper GG, Gustafsson JA, Hurd YL. Differential distribution and regulation of estrogen receptor-alpha and-beta mRNA within the female rat brain. Brain Res Mol Brain Res. 1998; 54(1):175–180. [PubMed: 9526077]
14. Mitra SW, Hoskin E, Yudkovitz J, Pear L, Wilkinson HA, Hayashi S, Pfaff DW, Ogawa S, Rohrer SP, Schaeffer JM, McEwen BS, Alves SE. Immunolocalization of estrogen receptor beta in the mouse brain: comparison with estrogen receptor alpha. Endocrinology. 2003; 144:2055–2067. [PubMed: 12697714]
15. Ogawa S, Eng V, Taylor J, Lubahn DB, Korach KS, Pfaff DW. Roles of estrogen receptor-alpha gene expression in reproduction-related behaviors in female mice. Endocrinology. 1998; 139:5070–5081. [PubMed: 9832446]
16. Musatov S, Chen W, Pfaff DW, Kaplitt MG, Ogawa S. RNAi-mediated silencing of estrogen receptor {alpha} in the ventromedial nucleus of hypothalamus abolishes female sexual behaviors. ProcNatlAcadSciUSA. 2006; 103:10456–10460.
17. Ogawa S, Chan J, Chester AE, Gustafsson JA, Korach KS, Pfaff DW. Survival of reproductive behaviors in estrogen receptor beta gene-deficient (betaERKO) male and female mice. ProcNatlAcadSciUSA. 1999; 96:12887–12892.
18. Bodo C, Rissman EF. New roles for estrogen receptor beta in behavior and neuroendocrinology. Front Neuroendocrinol. 2006; 27:217–232. [PubMed: 16603234]
19. Delaunay F, Pettersson K, Tujague M, Gustafsson JA. Functional differences between the amino-terminal domains of estrogen receptors alpha and beta. Mol Pharmacol. 2000; 58(3):584–590. [PubMed: 10953052]
20. Kastner P, Krust A, Turcotte B, Stropp U, Tora L, Gronemeyer H, Chambon P. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. EMBO Journal. 1990; 9:1603–1614. [PubMed: 2328727]
21. Vegeto E, Shahbaz MM, Wen DX, Goldman ME, O'Malley BW, McDonnell DP. Human progesterone receptor A form is a cell-and promoter-specific repressor of human progesterone receptor B function. Molecular Endocrinology. 1993; 7:1244–1255. [PubMed: 8264658]
22. Tung L, Kamel Mohamed M, Hoeffler JP, Takimoto GS, Horwitz KB. Antagonist-occupied human progesterone B-receptors activate transcription without binding to progesterone response elements and are dominantly inhibited by A-receptors. Molecular Endocrinology. 1993; 7:1256–1265. [PubMed: 8123133]
23. Giangrande PH, Pollio G, McDonnell DP. Mapping and characterization of the functional domains responsible for the differential activity of the A and B isoforms of the human progesterone receptor. Journal of Biological Chemistry. 1997; 272:32889–32900. [PubMed: 9407067]

24. Sartorius CA, Melville MY, Hovland AR, Tung L, Takimoto GS, Horwitz KB. A third transactivation function (AF3) of human progesterone receptors located in the unique N-terminal segment of the B-isoform. Molecular Endocrinology. 1994; 8:1347–1360. [PubMed: 7854352]
25. Mani SK, Reyna AM, Chen JZ, Mulac-Jericevic B, Conneely OM. Differential response of progesterone receptor isoforms in hormone-dependent and-independent facilitation of female sexual receptivity. Molecular Endocrinology. 2006; 20:1322–1332. [PubMed: 16484336]
26. Mulac-Jericevic B, Conneely OM. Reproductive tissue selective actions of progesterone receptors. Reproduction. 2004; 128:139–146. [PubMed: 15280552]
27. Pratt WB, Galigniana MD, Morishima Y, Murphy PJ. Role of molecular chaperones in steroid receptor action. Essays Biochem. 2004; 40:41–58. [PubMed: 15242338]
28. DeMarzo A, Beck CA, Oñate SA, Edwards DP. Dimerization of mammalian progesterone receptors occurs in the absence of DNA and is related to the release of the 90-kDa heat shock protein. Proceedings of the National Academy of Sciences USA. 1991; 88:72–76.
29. Klein-Hitpass L, Tsai SY, Weigel NL, Allan GF, Riley D, Rodriguez R, Schrader WT, Tsai MJ, O'Malley BW. The progesterone receptor stimulates cell-free transcription by enhancing the formation of a stable preinitiation complex. Cell. 1990; 60:247–257. [PubMed: 2153462]
30. Kininis M, Chen BS, Diehl AG, Isaacs GD, Zhang T, Siepel AC, Clark AG, Kraus WL. Genomic analyses of transcription factor binding, histone acetylation, and gene expression reveal mechanistically distinct classes of estrogen-regulated promoters. Mol Cell Biol. 2007; 27(14): 5090–5104. [PubMed: 17515612]
31. Pfaff D. Hormone-driven mechanisms in the central nervous system facilitate the analysis of mammalian behaviours. J Endocrinol. 2005; 184(3):447–453. [PubMed: 15749804]
32. Blaustein, JD.; Mani, SK. Feminine sexual behavior from neuroendocrine and molecular neurobiological perspectives. In: Blaustein, JD., editor. Handbook of Neurochemistry and Molecular Neurobiology. New York: Springer; 2006. p. 95-150.
33. Rosenfeld MG, Lunyak VV, Glass CK. Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response. Genes Dev. 2006; 20:1405–1428. [PubMed: 16751179]
34. O'Malley BW. Molecular biology. Little molecules with big goals. Science. 2006; 313:1749–1750. [PubMed: 16990541]
35. Lonard DM, Lanz RB, O'Malley BW. Nuclear receptor coregulators and human disease. Endocr Rev. 2007; 28(5):575–587. [PubMed: 17609497]
36. Torchia J, Rose DW, Inostroza J, Kamei Y, Westin S, Glass CK, Rosenfeld MG. The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function. Nature. 1997; 387:677–684. [PubMed: 9192892]
37. Oñate SA, Tsai SY, Tsai MJ, O'Malley BW. Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. Science. 1995; 270:1354–1357. [PubMed: 7481822]
38. McInerney EM, Tsai MJ, O'Malley BW, Katzenellenbogen BS. Analysis of estrogen receptor transcriptional enhancement by a nuclear hormone receptor coactivator. Proceedings of the National Academy of Sciences USA. 1996; 93:10069–10073.
39. Tanenbaum DM, Wang Y, Williams SP, Sigler PB. Crystallographic comparison of the estrogen and progesterone receptor's ligand binding domains. Proc Natl Acad Sci U S A. 1998; 95(11): 5998–6003. [PubMed: 9600906]
40. Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA, Greene GL. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell. 1998; 95(7):927–937. [PubMed: 9875847]
41. Oñate SA, Boonyaratanakornkit V, Spencer TE, Tsai SY, Tsai MJ, Edwards DP, O'Malley BW. The steroid receptor coactivator-1 contains multiple receptor interacting and activation domains that cooperatively enhance the activation function 1 (AF1) and AF2 domains of steroid receptors. Journal of Biological Chemistry. 1998; 273:12101–12108. [PubMed: 9575154]
42. Webb P, Nguyen P, Shinsako J, Anderson C, Feng W, Nguyen MP, Chen D, Huang SM, Subramanian S, McKinerney E, Katzenellenbogen BS, Stallcup MR, Kushner PJ. Estrogen receptor activation function 1 works by binding p160 coactivator proteins. Molecular Endocrinology. 1998; 12:1605–1618. [PubMed: 9773983]

43. Dutertre M, Smith CL. Ligand-independent interactions of p160/steroid receptor coactivators and CREB-Binding Protein (CBP) with estrogen receptor-à: Regulation by phosphorylation sites in the A/B region depends on other receptor domains. Molecular Endocrinology. 2003; 17:1296–1314. [PubMed: 12714702]
44. Voegel JJ, Heine MJS, Zechel C, Chambon P, Gronemeyer H. TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. EMBO Journal. 1996; 15:3667–3675. [PubMed: 8670870]
45. Hong H, Kohli K, Garabedian MJ, Stallcup MR. GRIP1, a transcriptional coactivator for the AF-2 transactivation domain of steroid, thyroid, retinoid, and vitamin D receptors. Molecular and Cellular Biology. 1997; 17:2735–2744. [PubMed: 9111344]
46. Anzick SL, Kononen J, Walker RL, Azorsa DO, Tanner MM, Guan XY, Sauter G, Kallioniemi OP, Trent JM, Meltzer PS. AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Science. 1997; 277:965–968. [PubMed: 9252329]
47. Suen CS, Berrodin TJ, Mastroeni R, Cheskis BJ, Lyttle CR, Frail DE. A transcriptional coactivator, steroid receptor coactivator-3, selectively augments steroid receptor transcriptional activity. Journal of Biological Chemistry. 1998; 273:27645–27653. [PubMed: 9765300]
48. Wu RC, Smith CL, O'Malley BW. Transcriptional regulation by steroid receptor coactivator phosphorylation. EndocrRev. 2005; 26:393–399.
49. Vasudevan N, Zhu YS, Daniel S, Koibuchi N, Chin WW, Pfaff D. Crosstalk between oestrogen receptors and thyroid hormone receptor isoforms results in differential regulation of the preproenkephalin gene. J Neuroendocrinol. 2001; 13(9):779–790. [PubMed: 11578528]
50. McKenna NJ, Nawaz Z, Tsai SY, Tsai MJ, O'Malley BW. Distinct steady-state nuclear receptor coregulator complexes exist in vivo. Proceedings of the National Academy of Sciences USA. 1998; 95:11697–11702.
51. Kamei Y, Xu L, Heinzel T, Torchia J, Kurokawa R, Gloss B, Lin SC, Heyman RA, Rose DW, Glass CK, Rosenfeld MG. A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. Cell. 1996; 85:403–414. [PubMed: 8616895]
52. Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, Evans RM. Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. Cell. 1997; 90:569–580. [PubMed: 9267036]
53. Chen D, Ma H, Hong H, Koh SS, Huang SM, Schurter BT, Aswad DW, Stallcup MR. Regulation of transcription by a protein methyltransferase. Science. 1999; 284:2174–2177. [PubMed: 10381882]
54. Xu J, Qiu Y, Demayo FJ, Tsai SY, Tsai MJ, O'Malley BW. Partial hormone resistance in mice with disruption of the steroid receptor coactivator-1 (SRC-1) gene. Science. 1998; 279:1922–1925. [PubMed: 9506940]
55. Weiss RE, Xu J, Ning G, Pohlenz J, O'Malley BW, Refetoff S. Mice deficient in the steroid receptor co-activator 1 (SRC-1) are resistant to thyroid hormone. EMBO J. 1999; 18:1900–1904. [PubMed: 10202153]
56. Nishihara E, Yoshida-Kimoya H, Chan C, Liao L, Davis RL, O'Malley BW, Xu J. SRC-1 null mice exhibit moderate motor dysfunction and delayed development of cerebellar Purkinje cells. The Journal of Neuroscience. 2003; 23:213–222. [PubMed: 12514218]
57. Wang Z, Qi C, Krones A, Woodring P, Zhu X, Reddy JK, Evans RM, Rosenfeld MG, Hunter T. Critical roles of the p160 transcriptional coactivators p/CIP and SRC-1 in energy balance. Cell Metab. 2006; 3(2):111–122. [PubMed: 16459312]
58. Gehin M, Mark M, Dennefeld C, Dierich A, Gronemeyer H, Chambon P. The function of TIF2/GRIP1 in mouse reproduction is distinct from those of SRC-1 and p/CIP. Molecular and Cellular Biology. 2002; 22:5923–5937. [PubMed: 12138202]
59. Mukherjee A, Amato P, Allred DC, DeMayo FJ, Lydon JP. Steroid receptor coactivator 2 is required for female fertility and mammary morphogenesis: insights from the mouse, relevance to the human. Nucl Recept Signal. 2007; 5:e011. [PubMed: 18174919]

60. Fernandez-Valdivia R, Mukherjee A, Amato P, Allred DC, Nguyen J, DeMayo FJ, Lydon JP. Progesterone-action in the murine uterus and mammary gland requires steroid receptor coactivator 2: relevance to the human. Front Biosci. 2007; 12:3640–3647. [PubMed: 17485327]
61. Jeong JW, Lee KY, Han SJ, Aronow BJ, Lydon JP, O'Malley BW, Demayo FJ. The p160 steroid receptor coactivator-2, SRC-2, regulates murine endometrial function and regulates progesterone-independent and-dependent gene expression. Endocrinology. 2007; 148(9):4238–4250. [PubMed: 17556502]
62. Li H, Gomes PJ, Chen JD. RAC3, a steroid/nuclear receptor-associated coactivator that is related to SRC-1 and TIF2. ProcNatlAcadSciUSA. 1997; 94:8479–8484.
63. Xu J, Liao L, Ning G, Yoshida-Kimoya H, Deng C, O'Malley BW. The steroid receptor coactivator SRC-3 (p/cip/RAC3/AIB1/ACTR/TRAM-1) is required for normal growth, puberty, female reproductive function, and mammary gland development. Proceedings of the National Academy of Sciences USA. 2000; 97:6379–6384.
64. Han SJ, Demayo FJ, Xu J, Tsai SY, Tsai MJ, O'Malley BW. Steroid receptor coactivator (SRC)-1 and SRC-3 differentially modulate tissue-specific activation functions of the progesterone receptor. MolEndocrinol. 2006; 20:45–55.
65. An BS, Selva DM, Hammond GL, Rivero-Muller A, Rahman N, Leung PC. Steroid receptor coactivator-3 is required for progesterone receptor trans-activation of target genes in response to gonadotropin-releasing hormone treatment of pituitary cells. J Biol Chem. 2006; 281(30):20817–20824. [PubMed: 16728408]
66. Chrivia JC, Kwok RP, Lamb N, Hagiwara M, Montminy MR, Goodman RH. Phosphorylated CREB binds specifically to the nuclear protein CBP. Nature. 1993; 365:855–859. [PubMed: 8413673]
67. Kwok RPS, Lundblad JR, Chrivia JC, Richards JP, Bachinger HP, Brennan RG, Roberts SGE, Green MR, Goodman RH. Nuclear protein CBP is a coactivator for the transcription factor CREB. Nature. 1994; 370:223–229. [PubMed: 7913207]
68. Yang XJ, Ogryzko VV, Nishikawa J, Howard BH, Nakatani Y. A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. Nature. 1996; 382:319–324. [PubMed: 8684459]
69. Smith CL, Oñate SA, Tsai MJ, O'Malley BW. CREB binding protein acts synergistically with steroid receptor coactivator-1 to enhance steroid receptor-dependent transcription. Proceedings of the National Academy of Sciences USA. 1996; 93:8884–8888.
70. Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van OGJ, Goodman RH, Peters DJ. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature. 1995; 376:348–351. [PubMed: 7630403]
71. Oike Y, Hata A, Mamiya T, Kaname T, Noda Y, Suzuki M, Yasue H, Nabeshima T, Araki K, Yamamura K. Truncated CBP protein leads to classical Rubinstein-Taybi syndrome phenotypes in mice: implications for a dominant-negative mechanism. HumMolGenet. 1999; 8:387–396.
72. Tetel MJ, Giangrande PH, Leonhardt SA, McDonnell DP, Edwards DP. Hormone-dependent interaction between the amino-and carboxyl-terminal domains of progesterone receptor in vitro and in vivo. Molecular Endocrinology. 1999; 13:910–924. [PubMed: 10379890]
73. Liu Z, Wong J, Tsai SY, Tsai MJ, O'Malley BW. Sequential recruitment of steroid receptor coactivator-1 (SRC-1) and p300 enhances progesterone receptor-dependent initiation and reinitiation of transcription from chromatin. ProcNatlAcadSciUSA. 2001; 98:12426–12431.
74. Xu Y, Klein-Hitpass L, Bagchi MK. E1A-mediated repression of progesterone receptor-dependent transactivation involves inhibition of the assembly of a multisubunit coactivation complex. Mol Cell Biol. 2000; 20(6):2138–2146. [PubMed: 10688660]
75. Cavarretta ITR, Mukopadhyay R, Lonard DM, Cowsert LM, Bennet CF, O'Malley B, Smith CL. Reduction of coactivator expression by antisense oligodeoxynucleotides inhibits ERa transcriptional activity and MCF-7 proliferation. Molecular Endocrinology. 2002; 16(2):253–269. [PubMed: 11818499]
76. Lanz RB, McKenna NJ, Oñate SA, Albrecht U, Wong J, Tsai SY, Tsai MJ, O'Malley BW. A steroid receptor coactivator, SRA, functions as an RNA and is present in an SRC-1 complex. Cell. 1999; 97:17–27. [PubMed: 10199399]

77. Lanz RB, Chua SS, Barron N, Soder BM, DeMayo F, O'Malley BW. Steroid receptor RNA activator stimulates proliferation as well as apoptosis in vivo. Molecular and Cellular Biology. 2003; 23:7163–7176. [PubMed: 14517287]

78. Shao W, Halachmi S, Brown M. ERAP140, a conserved tissue-specific nuclear receptor coactivator. Molecular and Cellular Biology. 2002; 22:3358–3372. [PubMed: 11971969]

79. Ito M, Yuan CX, Malik S, Gu W, Fondell JD, Yamamura S, Fu ZY, Zhang X, Qin J, Roeder RG. Identity between TRAP and SMCC complexes indicates novel pathways for the function of nuclear receptors and diverse mammalian activators. Mol Cell. 1999; 3(3):361–370. [PubMed: 10198638]

80. Tcherepanova I, Puigserver P, Norris JD, Spiegelman BM, McDonnell DP. Modulation of Estrogen Receptor-alpha Transcriptional Activity by the Coactivator PGC-1. Journal of Biological Chemistry. 2000; 275:16302–16308. [PubMed: 10748020]

81. Boonyaratanakornkit V, Melvin V, Prendergast P, Altmann M, Ronfani L, Bianchi ME, Taraseviciene L, Nordeen SK, Allegretto EA, Edwards DP. High-mobility group chromatin proteins 1 and 2 functionally interact with steroid hormone receptors to enhance their DNA binding in vitro and transcriptional activity in mammalian cells. Molecular and Cellular Biology. 1998; 18(8):4471–4487. [PubMed: 9671457]

82. Brady ME, Ozanne DM, Gaughan L, Waite I, Cook S, Neal DE, Robson CN. Tip60 is a nuclear hormone receptor coactivator. J Biol Chem. 1999; 274(25):17599–17604. [PubMed: 10364196]

83. O'Malley BW. Coregulators: from whence came these "master genes". MolEndocrinol. 2007; 21:1009–1013.

84. Misiti S, Schomburg L, Yen PM, Chin WW. Expression and hormonal regulation of coactivator and corepressor genes. Endocrinology. 1998; 139:2493–2500. [PubMed: 9564863]

85. Shearman LP, Zylka MJ, Reppert SM, Weaver DR. Expression of basic helix-loop-helix/PAS genes in the mouse suprachiasmatic nucleus. Neuroscience. 1999; 89:387–397. [PubMed: 10077321]

86. Martinez de Arrieta C, Koibuchi N, Chin WW. Coactivator and corepressor gene expression in rat cerebellum during postnatal development and the effect of altered thyroid status. Endocrinology. 2000; 141:1693–1698. [PubMed: 10803578]

87. Meijer OC, Steenbergen PJ, de Kloet ER. Differential expression and regional distribution of steroid receptor coactivators SRC-1 and SRC-2 in brain and pituitary. Endocrinology. 2000; 141:2192–2199. [PubMed: 10830308]

88. Auger AP, Tetel MJ, McCarthy MM. Steroid receptor coactivator-1 mediates the development of sex specific brain morphology and behavior. Proceedings of the National Academy of Sciences USA. 2000; 97:7551–7555.

89. Molenda HA, Griffin AL, Auger AP, McCarthy MM, Tetel MJ. Nuclear receptor coactivators modulate hormone-dependent gene expression in brain and female reproductive behavior in rats. Endocrinology. 2002; 143:436–444. [PubMed: 11796496]

90. Ogawa H, Nishi M, Kawata M. Localization of nuclear coactivators p300 and steroid receptor coactivator 1 in the rat hippocampus. Brain Research. 2001; 890:197–202. [PubMed: 11164785]

91. Charlier TD, Lakaye B, Ball GF, Balthazart J. Steroid receptor coactivator SRC-1 exhibits high expression in steroid-sensitive brain areas regulating reproductive behaviors in the quail brain. Neuroendocrinology. 2002; 76:297–315. [PubMed: 12457041]

92. Tetel MJ, Siegal NK, Murphy SD. Cells in behaviourally relevant brain regions coexpress nuclear receptor coactivators and ovarian steroid receptors. J Neuroendocrinol. 2007; 19(4):262–271. [PubMed: 17244199]

93. Blaustein JD, Turcotte JC. Estradiol-induced progestin receptor immunoreactivity is found only in estrogen receptor-immunoreactive cells in guinea pig brain. Neuroendocrinology. 1989; 49:454–461. [PubMed: 2657476]

94. Warembourg M, Jolivet A, Milgrom E. Immunohistochemical evidence of the presence of estrogen and progesterone receptors in the same neurons of the guinea pig hypothalamus and preoptic area. Brain Res. 1989; 480:1–15. [PubMed: 2713643]

95. Camacho-Arroyo I, Neri-Gomez T, Gonzalez-Arenas A, Guerra-Araiza C. Changes in the content of steroid receptor coactivator-1 and silencing mediator for retinoid and thyroid hormone receptors

in the rat brain during the estrous cycle. The Journal of Steroid Biocheminstry and Molecular Biology. 2005; 94:267–272.

96. Mitev YA, Wolf SS, Almeida OF, Patchev VK. Developmental expression profiles and distinct regional estrogen responsiveness suggest a novel role for the steroid receptor coactivator SRC-l as a discriminative amplifier of estrogen signaling in the rat brain. The FASEB Journal. 2003; 17:518–519. [PubMed: 12551846]
97. Charlier TD, Ball GF, Balthazart J. Plasticity in the expression of the steroid receptor coactivator-1 in the Japanese quail brain: Effect of sex, testosterone, stress and time of the day. Neuroscience. 2006; 172:333–343.
98. Iannacone EA, Yan AW, Gauger KJ, Dowling ALS, Zoeller RT. Thyroid hormone exerts site-specific effects on SRC-1 and NCoR expression selectively in the neonatal rat brain. Molecular and Cellular Endocrinology. 2002; 186:49–59. [PubMed: 11850121]
99. Ramos HE, Weiss RE. Regulation of nuclear coactivator and corepressor expression in mouse cerebellum by thyroid hormone. Thyroid. 2006; 16(3):211–216. [PubMed: 16571082]
100. Maerkel K, Durrer S, Henseler M, Schlumpf M, Lichtensteiger W. Sexually dimorphic gene regulation in brain as a target for endocrine disrupters: developmental exposure of rats to 4-methylbenzylidene camphor. Toxicol Appl Pharmacol. 2007; 218(2):152–165. [PubMed: 17188730]
101. McGinnis MY, Lumia AR, Tetel MJ, Molenda-Figuiera HA, Possidente B. Effects of androgenic steroids on the development and expression of running wheel activity and circadian rhythms in male rats. Physiology and Behavior. 2007; 92:1010–1018. [PubMed: 17716697]
102. Tetel MJ, Ungar TC, Hassan B, Bittman EL. Photoperiodic regulation of androgen receptor and steroid receptor coactivator-1 in Siberian hamster brain. Molecular Brain Research. 2004; 131:79–87. [PubMed: 15530655]
103. Bousios S, Karandrea D, Kittas C, Kitraki E. Effects of gender and stress on the regulation of steroid receptor coactivator-1 expression in the rat brain and pituitary. The Journal of Steroid Biocheminstry and Molecular Biology. 2001; 78:401–407.
104. Meijer OC, van der LS, Lachize S, Steenbergen PJ, de Kloet ER. Steroid receptor coregulator diversity: what can it mean for the stressed brain? Neuroscience. 2006; 138:891–899. [PubMed: 16310313]
105. Sodersten P. Effects of anti-oestrogen treatment of neonatal male rats on lordosis behaviour and mounting behaviour in the adult. JEndocrinol. 1978; 76:241–249. [PubMed: 627818]
106. Whalen RE, Edwards DA. Hormonal determinants of the development of masculine and feminine behavior in male and female rats. AnatRec. 1967; 157:173–180.
107. McCarthy MM, Schlenker EH, Pfaff DW. Enduring consequences of neonatal treatment with antisense oligodeoxynucleotides to estrogen receptor messenger ribonucleic acid on sexual differentiation of rat brain. Endocrinology. 1993; 133:433–439. [PubMed: 8344188]
108. Auger AP, Perrot-Sinai TS, Auger CJ, Ekas LA, Tetel MJ, McCarthy MM. Expression of the nuclear receptor coactivator, cAMP response element-binding protein, is sexually dimorphic and modulates sexual differentiation of neonatal rat brain. Endocrinology. 2002; 143:3009–3016. [PubMed: 12130567]
109. Apostolakis EM, Ramamurphy M, Zhou D, Onate S, O'Malley B. Acute disruption of select steroid receptor coactivators prevents reproductive behavior in rats and unmasks genetic adaptation in knockout mice. Molecular Endocrinology. 2002; 16:1511–1523. [PubMed: 12089347]
110. Pleim ET, Brown TJ, MacLusky NJ, Etgen AM, Barfield RJ. Dilute estradiol implants and progestin receptor induction in the ventromedial nucleus of the hypothalamus: correlation with receptive behavior in female rats. Endocrinology. 1989; 124:1807–1812. [PubMed: 2924724]
111. Grenier J, Trousson A, Chauchereau A, Cartaud J, Schumacher M, Massaad C. Differential recruitment of p160 coactivators by glucocorticoid receptor between Schwann cells and astrocytes. Molecular Endocrinology. 2005; 20:254–267. [PubMed: 16179382]
112. van der Laan S, Lachize SB, Vreugdenhil E, de Kloet ER, Meijer OC. Nuclear receptor coregulators differentially modulate induction and glucocorticoid receptor-mediated repression of

the corticotropin-releasing hormone gene. Endocrinology. 2008; 149(2):725–732. [PubMed: 18006628]

113. Molenda-Figueira HA, Williams CA, Griffin AL, Rutledge EM, Blaustein JD, Tetel MJ. Nuclear receptor coactivators function in estrogen receptor-and progestin receptor-dependent aspects of sexual behavior in female rats. Hormones and Behavior. 2006; 50:383–392. [PubMed: 16769066]
114. Hardy DF, DeBold JF. The relationship between levels of exogenous hormones and the display of lordosis by the female rat. HormsBehav. 1971; 2:287–297.
115. Whalen RE. Estrogen-progesterone induction of mating in female rats. HormBehav. 1974; 5:157–162.
116. Tennent BJ, Smith ER, Davidson JM. The effects of estrogen and progesterone on female rat proceptive behavior. HormsBehav. 1980; 14:65–75.
117. Edwards DA, Pfeifle JK. Hormonal control of receptivity, proceptivity and sexual motivation. PhysiolBehav. 1983; 30:437–443.
118. Erskine MS. Solicitation behavior in the estrous female rat: A review. HormsBehav. 1989; 23:473–502.
119. Ogawa S, Olazabal UE, Parhar IS, Pfaff DW. Effects of intrahypothalamic administration of antisense DNA for progesterone receptor mRNA on reproductive behavior and progesterone receptor immunoreactivity in female rat. JNeurosci. 1994; 14:1766–1774. [PubMed: 8126569]
120. Molenda-Figueira HA, Murphy SD, Shea KL, Siegal NK, Zhao Y, Chadwick JG, Denner LA, Tetel MJ. Steroid receptor coactivator-1 from brain physically interacts differentially with steroid receptor subtypes. Endocrinology. 2008; 149(10):5272–5279. [PubMed: 18566116]
121. Kudwa AE, Rissman EF. Double oestrogen receptor alpha and beta knockout mice reveal differences in neural oestrogen-mediated progestin receptor induction and female sexual behaviour. J Neuroendocrinol. 2003; 15(10):978–983. [PubMed: 12969243]
122. Fugger HN, Foster TC, Gustafsson J, Rissman EF. Novel effects of estradiol and estrogen receptor alpha and beta on cognitive function. Brain Res. 2000; 883(2):258–264. [PubMed: 11074057]
123. Isgor C, Cecchi M, Kabbaj M, Akil H, Watson SJ. Estrogen receptor beta in the paraventricular nucleus of hypothalamus regulates the neuroendocrine response to stress and is regulated by corticosterone. Neuroscience. 2003; 121(4):837–845. [PubMed: 14580933]
124. Margeat E, Poujol N, Boulahtouf A, Chen Y, Muller JD, Gratton E, Cavailles V, Royer CA. The human estrogen receptor alpha dimer binds a single SRC-1 coactivator molecule with an affinity dictated by agonist structure. Journal of Molecular Biology. 2001; 306:433–442. [PubMed: 11178903]
125. Smith CL, Nawaz Z, O'Malley BW. Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. Molecular Endocrinology. 1997; 11:657–666. [PubMed: 9171229]
126. Yi P, Driscoll MD, Huang J, Bhagat S, Hilf R, Bambara RA, Muyan M. The effects of estrogen-responsive element-and ligand-induced structural changes on the recruitment of cofactors and transcriptional responses by ER alpha and ER beta. Molecular Endocrinology. 2002; 16:674–693. [PubMed: 11923465]
127. Dutertre M, Smith CL. Ligand-independent interactions of p160/steroid receptor coactivators and CREB-binding protein (CBP) with estrogen receptor-alpha: regulation by phosphorylation sites in the A/B region depends on other receptor domains. MolEndocrinol. 2003; 17:1296–1314.
128. Tremblay A, Tremblay GB, Labrie F, Giguere V. Ligand-independent recruitment of SRC-1 to estrogen receptor beta through phosphorylation of activation function AF-1. MolCell. 1999; 3:513–519.
129. Wong C, Komm B, Cheskis BJ. Structure-Function evaluation of ER alpha and beta interplay with SRC family coactivators. ER selective ligands. Biochemistry. 2001; 40:6756–6765. [PubMed: 11389589]
130. Monroe DG, Johnsen SA, Subramaniam M, Getz BJ, Khosla S, Riggs BL, Spelsberg TC. Mutual antagonism of estrogen receptors alpha and beta and their preferred interactions with steroid

receptor coactivators in human osteoblastic cell lines. JEndocrinol. 2003; 176:349–357. [PubMed: 12630920]

131. Cowley SM, Parker MG. A comparison of transcriptional activation by ER alpha and ER beta. J Steroid Biochem Mol Biol. 1999; 69(1–6):165–175. [PubMed: 10418990]
132. Rissman EF, Early AH, Taylor JA, Korach KS, Lubahn DB. Estrogen receptors are essential for female sexual receptivity. Endocrinology. 1997; 138:507–510. [PubMed: 8977441]
133. Auger CJ, Bentley GE, Auger AP, Ramamurthy M, Ball GF. Expression of cAMP response element binding protein-binding protein in the song control system and hypothalamus of adult European starlings (Sturnus vulgaris). Journal of Neuroendocrinology. 2002; 14:805–813. [PubMed: 12372005]
134. Duncan KA, Carruth LL. The sexually dimorphic expression of L7/SPA, an estrogen receptor coactivator, in zebra finch telencephalon. Dev Neurobiol. 2007
135. Charlier TD, Ball GF, Balthazart J. Inhibition of steroid receptor coactivator-1 blocks estrogen and androgen action on male sex behavior and associated brain plasticity. Journal of Neuroscience. 2005; 25:906–913. [PubMed: 15673671]
136. Charlier TD, Harada N, Ball GF, Balthazart J. Targeting steroid receptor coactivator-1 expression with locked nucleic acids antisense reveals different thresholds for the hormonal regulation of male sexual behavior in relation to aromatase activity and protein expression. Behav Brain Res. 2006; 172(2):333–343. [PubMed: 16797739]

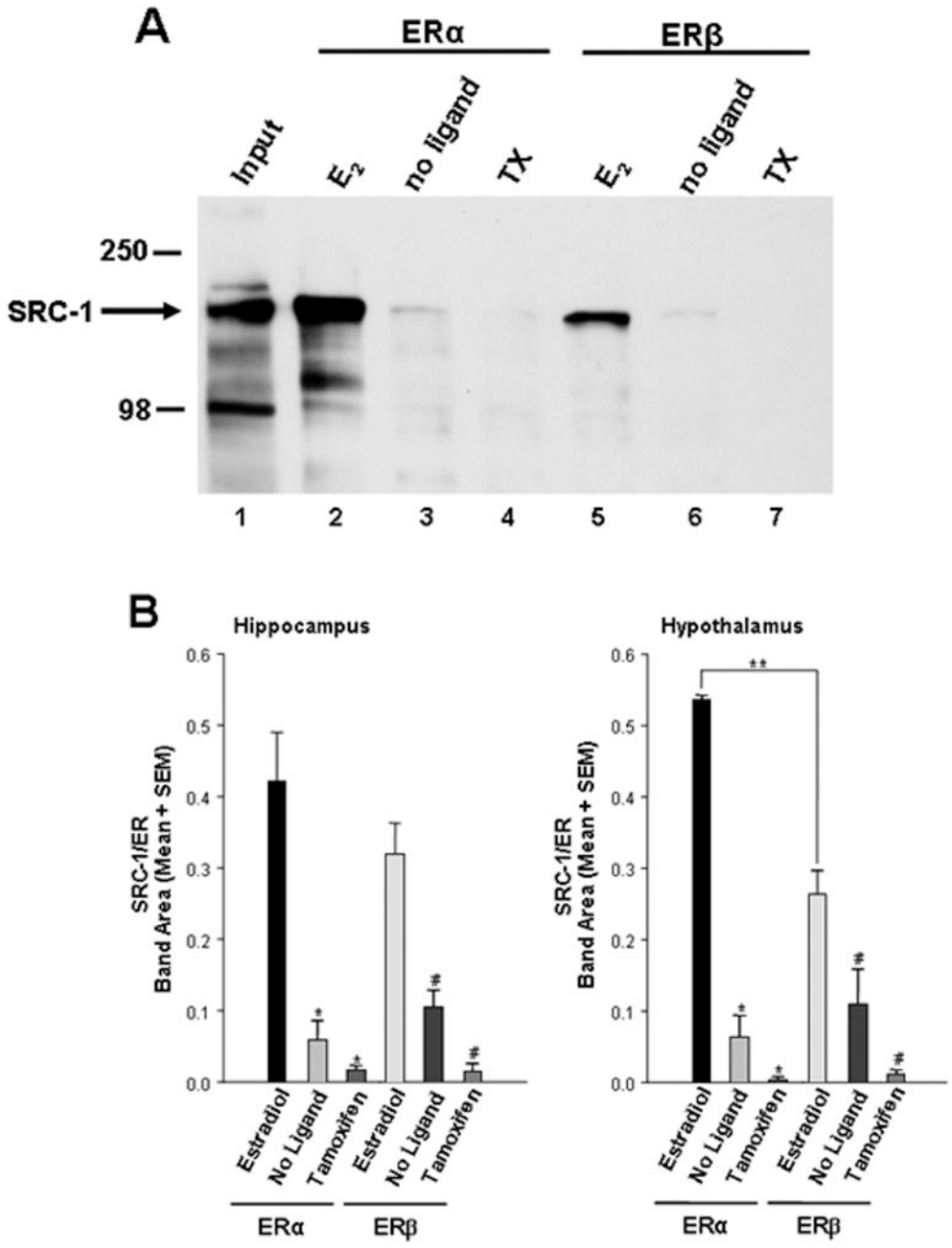

Figure 1. SRC-1 from rat brain associates with ERα and ERβ in a ligand-dependent and receptor isoform-specific manner

A) SRC-1 from the hypothalamus associates with ERα and ERβ in the presence of estradiol (lanes 2 and 5), but not in the absence of ligand (lanes 3 and 6), or in the presence of the SERM, tamoxifen (lanes 4 and 7). Input (1% of total) of SRC-1 from hypothalamic extract is shown in Lane 1.

B) In the presence of estradiol, both ERα and ERβ interacted with hippocampal SRC-1, but little to no interactions were detected in the absence of ligand or when receptors were bound to Tamoxifen. Hypothalamic SRC-1 interacted more strongly with ERα than ERβ in the presence of estradiol * $p < 0.0001$, significantly different from ERα + estradiol. # $p < 0.01$,

significantly different from ERβ + estradiol. ** $p < 0.05$, *t*-test, n = 4–5 per treatment group. From (120), Copyright 2008, The Endocrine Society.