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Minireview

Nuclear Receptor Coactivator Function in Reproductive Physiology and Behavior[1]

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ABSTRACT

Gonadal steroid hormones act throughout the body to elicit changes in gene expression that result in profound effects on reproductive physiology and behavior. Steroid hormones exert many of these effects by binding to their respective intracellular receptors, which are members of a nuclear receptor superfamily of transcriptional activators. A variety of in vitro studies indicate that nuclear receptor coactivators are required for efficient transcriptional activity of steroid receptors. Many of these coactivators are found in a variety of steroid hormone-responsive reproductive tissues, including the reproductive tract, mammary gland, and brain. While many nuclear receptor coactivators have been investigated in vitro, we are only now beginning to understand their function in reproductive physiology and behavior. In this review, we discuss the general mechanisms of action of nuclear receptor coactivators in steroid-dependent gene transcription. We then review some recent and exciting findings on the function of nuclear receptor coactivators in steroid-dependent brain development and reproductive physiology and behavior.

behavior, hypothalamus, neuroendocrinology, steroid hormone receptors

ROLE OF STEROID HORMONES IN BRAIN DEVELOPMENT AND REPRODUCTIVE BEHAVIOR

Organizational Effects of Steroid Hormones

Steroid hormones have profound effects on development, growth, and reproduction. Most of these effects can be classified as organizational and activational effects. Organizational effects occur prior (or just after) birth and are usually permanent, while activational effects occur long after birth (usually in adulthood) and are often transient. Reproductive physiology and behavior in adults require the appropriate hormone-dependent development of reproductive organs and specific neural substrates. A classic example of hormonal influences on sexual differentiation of the brain is the development of the sexually dimorphic nucleus of the preoptic area (SDN-POA), a hypothalamic region involved in the control of adult sexual behavior in rodents [1]. In males, this nucleus is three to four times larger in volume and contains a greater density of cells than in females [1]. Castration of male rats on the day of birth reduces the size of the SDN [2]. Testosterone (T) administration to female rat pups during the first week of life will increase the volume of this nucleus to that of normal males [2]. A variety of studies have revealed that these effects of testosterone on the SDN-POA are due to the conversion of T to estradiol (E) by the enzyme aromatase [3, 4]. Aromatase is found in a variety of brain areas, including the POA [5], which is the primary neural structure that controls male sexual behavior in rodents [6, 7].

The T surge in males just after birth also suppresses the development of female sexual behavior in adulthood [8, 9]. This suppression of female sexual behavior is due to E, aromatized from T, binding to ER [10]. In addition, the development of masculine sexual behavior in the adult male rat is dependent on this T surge and is mediated by androgen receptors [11, 12]. In adult male rats that were castrated and treated with either T or E, no differences were found in the number of mounts or intromissions. Interestingly, rats receiving T ejaculated more frequently than those treated with E [13, 14]. These findings suggest that while E does not elicit full male sexual behavior alone, many of the effects of T on brain and behavior are mediated by its conversion to E.

Activational Effects of Steroid Hormones

The ovarian steroid hormones E and progesterone (P) act in the brain to regulate female sexual behavior in rodents [15]. During the 4–5-day rat estrous cycle, follicle stimulating hormone acts at the ovaries to induce an estrogen peak on the day of proestrus [16, 17]. This peak in E is followed by a rise in luteinizing hormone (LH), which causes ovulation [16, 17]. Approximately 48 h after the E peak, the corpus luteum begins to produce P, and estrous behaviors begin [18, 19].

In rodents, E is necessary for sexual receptivity, which is characterized by the lordosis posture [20, 21]. This well-defined posture consists of the female arching the back and raising the head and hindquarters in response to mounting by a male [22]. Ovariectomy eliminates lordosis, while administration of E, followed by P, to mimic the estrous cycle, induces the expression of lordosis [20, 21, 23]. One physiological function of E is to induce progestin receptors (PR) in the brain and other reproductive tissues [24–28].

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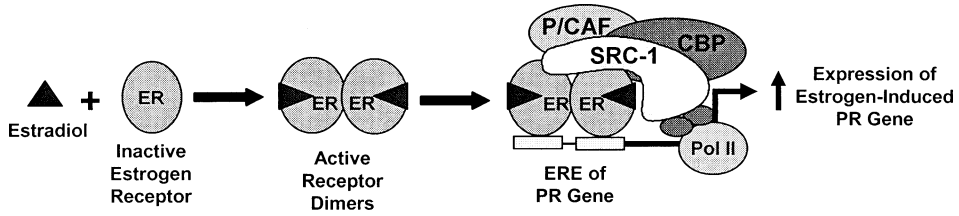

FIG. 1. Mechanism of ER-mediated transactivation of PR gene. Estradiol binds to an inactive estrogen receptor (ER). The receptor then undergoes a conformational change that activates the receptor and allows it to dimerize with another active ER. The dimer complex translocates to the nucleus of the cell, where it binds to an estrogen-responsive element on target genes and initiates gene transcription. ERE, estrogen response element; SRC-1, steroid receptor coactivator-1; CBP, CREB binding protein; P/CAF, p300/CBP-associated factor; PR, progestin receptor.

While high doses of E alone can facilitate receptive behaviors in female rats [29], the full repertoire of estrous behaviors requires the presence of circulating P [20, 21, 30, 31]. For example, P stimulates proceptive behaviors, including hopping, darting, and ear wiggling [20, 32, 33], that serve to solicit interactions with a male and initiate mating. Ovariectomized rats treated with E and increasing doses of P have more frequent solicitations of males and remain in proximity to males longer than females that lack P [33].

Testosterone, produced by the testes, is required for the expression of masculine sexual behaviors in rodents [34]. In rats, masculine sex behaviors begin to develop by 45 days of age but are not fully expressed until T peaks at the time of puberty, around 65 days of age [35]. Three main behaviors make up the repertoire of male sex behavior in rodents during a mating bout: 1) the male mounts a female frequently; 2) after several repeated mounts, the male will then intromit the female; and 3) within 10–15 intromissions, the male ejaculates [35].

STEROID HORMONE RECEPTORS

Mechanism of Steroid Hormone Action

Steroid hormones exert their biological effects by binding to their respective intracellular receptors, which are members of a nuclear receptor superfamily of transcriptional activators [36]. Type I steroid receptors bind to DNA in the presence of ligand and include the receptors for estrogens (ER), progestins (PR), androgens (AR), glucocorticoids, and mineralocorticoids [36, 37]. Type II steroid receptors, which include thyroid hormone receptor (TR) and vitamin D receptor (VDR), interact with DNA in the absence of ligand [36, 37]. Steroid receptors possess two main transactivation domains, the AF-1 located in the N-terminus and the AF-2 located in the C-terminal ligand binding domain of the receptor [36, 37]. Steroid receptors also contain a central DNA binding domain, which is highly conserved among the steroid receptor family [36, 37].

On binding hormone, Type I receptors undergo a conformational change transforming the receptors to the active form [38]. Dissociation of heat shock protein 90 and other immunophillins allows the activated receptors to dimerize [39]. The dimer complex is translocated to the nucleus, where it binds to hormone responsive elements in target genes to alter the rate of transcription [39, 40]. Steroid receptors are phosphoproteins, in which phosphorylation, by ligand binding and other events, increases transcriptional activation of the receptor [41, 42]. As stated previously, one well-known example of this steroid receptor transactivation is ER-mediated induction of PR gene expression. Estradiol-bound ER dimers bind to the estrogen response element in the promoter of the PR gene to induce PR expression (Fig. 1) [43–45].

Role of Steroid Receptors in Female Reproductive Behavior

A variety of implant studies reveal that steroid hormones act in the brain to influence reproductive behavior [23, 31, 46, 47]. The ovarian steroid receptors ER and PR are found in a number of hypothalamic brain regions, including the mPOA, arcuate nucleus, and ventromedial nucleus (VMN) [48], as well as many extrahypothalamic regions, including the hippocampus, cortex, amygdala, and midbrain central gray [48, 49]. Neural ER are essential for the expression of female reproductive behavior in rodents [50, 51]. The VMN contains a high density of ER and appears to be the most sensitive site for estrogen-dependent reproductive behaviors [46, 52]. Lesions of the VMN inhibit the display of lordosis [53]. Estradiol implants into the VMN facilitate estrous behavior in female rodents [46, 47], while antiestrogens implanted into this region inhibit lordosis [54]. Thus, estradiol action in the VMN is critical for the display of female sexual behavior.

ER exist in two forms, α and β [55], which are both necessary for normal reproductive behavior [50, 51]. Female ERα knockout mice are infertile because of polycystic ovaries [56] and do not display receptive behaviors when treated with E [50]. In contrast, ERβ knockout mice express higher levels of receptive behaviors than wild-type mice and are receptive even after the day of estrus [51]. Furthermore, while ERβ knockouts are fertile, they tend to have smaller litters of pups than wild-type mice [57]. Female mice lacking both ERα and ERβ (ER$\alpha\beta$KO) are infertile, although development of reproductive tracts are normal [56, 58]. This infertility may be caused by several factors in female ER$\alpha\beta$KO mice, including polycystic ovaries and the abnormal presence of Sertoli cells in these female mice [56, 58]. These findings suggest that ERα is the isoform that predominantly regulates reproductive behavior and physiology in rodents, while ERβ seems to play a less crucial role in reproduction.

PR are also expressed in many behaviorally relevant brain sites, including the VMN, midbrain central gray, mPOA, amygdala, and cortex [59–61]. Estradiol induces PR expression in the mPOA and VMN [24, 25, 46, 62], sites known to regulate hormone-dependent female reproductive behavior [23, 63]. Furthermore, E induction of PR in the VMN is required for full expression of reproductive behaviors [46, 49]. Progesterone implants into the VMN facilitate reproductive behaviors, while antiprogestins eliminate these behaviors [23, 31]. Likewise, treatment with PR antisense directed at the VMN reduces both proceptive and receptive behaviors [32, 64, 65]. PR is expressed in two forms, the full-length PR-B and the truncated PR-A [66]. In vitro studies indicate that PR-B is a stronger transcriptional activator than PR-A [67–69]. In support of a role for

PR-B in female reproductive behavior, homozygous PR-B knockout mice are infertile and display lower levels of lordosis than heterozygotes or wild-type mice [70]. Deletion of the truncated PR-A isoform in female mice also leads to infertility and lack of lordosis posturing [71, 72]. Thus, the functional differences of the two PR forms in vivo need to be investigated further.

NUCLEAR RECEPTOR COACTIVATORS

Nuclear Receptor Coactivator Action

Nuclear receptor coactivators have recently been shown to dramatically enhance the activity of nuclear receptors in vitro, including the steroid receptors ER, PR, AR, and glucocorticoid receptor [49, 73–75]. As detailed by McKenna et al. [73], there are several criteria that define a nuclear receptor coactivator. Nuclear receptor coactivators physically associate with receptors in a ligand-dependent manner [73, 74]. Receptor agonists promote, while antagonists prevent, these receptor-coactivator interactions. For example, selective estrogen receptor modulators (SERMs) block E-dependent recruitment of coactivators to ERα and ERβ, suggesting a mechanism for these ER antagonists [76]. Nuclear receptor coactivators usually interact with the C-terminal AF-2 of the receptor [73, 77–79] (but compare [80]). This physical interaction between coactivator and ligand-bound receptor appears to be mediated by the LXXLL domain, or nuclear receptor (NR) box, which is a domain common to all nuclear receptor coactivators [73]. Nuclear receptor coactivators promote gene expression by bridging the receptor complex with the basal transcription machinery and inducing chromatin remodeling through their intrinsic histone acetyltransferase activity [73, 81, 82]. Histone acetyltransferases disrupt interactions between the nucleosome and DNA, allowing coactivators more efficient access to the gene promoter, thus facilitating transcriptional activation [81, 83]. In vitro studies using antibodies against nuclear receptor coactivators indicate that coactivators are rate limiting in steroid receptor-mediated gene transcription [84]. 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 [74]. While the list of nuclear receptor coactivators is growing rapidly [85, 86], this review focuses on coactivators that modulate reproductively relevant steroid hormone receptor functions in the brain.

The SRC Family of Nuclear Receptor Coactivators

The p160 family of nuclear receptor coactivators include Steroid Receptor Coactivator-1 (SRC-1, also referred to as NCoA-1) [74], SRC-2 (NCoA-2/GRIP-1/TIF-2) [78, 87] and SRC-3 (RAC3/AIB1/pCIP/ACTR/TRAM1) [88, 89]. SRC-1 was the first coactivator of steroid receptors to be discovered [74]. In vitro, SRC-1 enhances the transcriptional activity of a variety of nuclear receptors, including ER and PR, in a ligand-dependent manner [74, 90]. It is thought that ligand-bound steroid receptors recruit coactivators, such as SRC-1, to facilitate binding to their respective hormone response elements [74, 79, 91, 92] (and see Fig. 1). While the SRC family of nuclear receptor coactivators interacts with a variety of steroid receptors, recent studies indicate that the efficiency of these interactions is dependent on the isoform of the steroid receptor. ERα was found to have higher affinities for SRC-1 and SRC-3 than ERβ [90]. Furthermore, this study found that ERα preferentially interacted with SRC-3 over SRC-1 [90]. PR-B interacts more efficiently with SRC-1 than does PR-A [93], which may explain the in vitro studies suggesting that PR-B is a stronger transcriptional activator than PR-A [67–69]. The possible functional differences between the SRC coactivators in vivo are discussed later.

CREB Binding Protein

CREB binding protein (CBP) was initially discovered to be a transcriptional activator of cAMP-response element binding protein (CREB) [94, 95]. More recently, CBP has been found to function as an integrator of nuclear receptors with other cell signaling pathways, including CREB and AP-1 [95, 96]. As is the case with the SRC family, CBP is important in ligand-dependent transcriptional activity of nuclear receptors, including ER and PR [91]. Interestingly, mutation of the CBP gene causes Rubinstein-Taybi syndrome, which results in severe mental retardation and a variety of physiological deformities in humans [97]. In mice, mutations of CBP lead to similar physical deformities as well as impaired memory [98]. While p300 is closely related to CBP, genetic knockout mice for CBP and p300 exhibit different phenotypes, suggesting a functional distinction between these coactivators [99].

A variety of in vitro studies indicate that SRC-1 and CBP act synergistically to enhance ER transcriptional activity [91]. In support of this concept, in vitro studies indicate that SRC-1 physically interacts with CBP and recruits CBP to the coactivator complex [67, 91, 96]. ERα requires interaction with both SRC-1 and CBP for full transcriptional activity, and prevention of these interactions by polypeptides blocks ERα transcription [83]. P/CAF is another coactivator that interacts with ER, SRC-1, and CBP and may complex with SRC-1 and CBP to enhance ER activity [100]. As is the case with ER, PR also requires both SRC-1 and CBP for full transcriptional activity and function [67, 101, 102]. For ligand-bound PR to induce transcription of target genes, SRC-1 must be recruited to the receptor dimer complex first, followed by CBP [101]. Deletion of either the CBP/p300 binding site or the C-terminal region containing the PR binding site of SRC-1 dramatically reduces PR transactivation [101].

Other Coactivators of Steroid Receptors

The SRC family and CBP are only a few of the coactivators that have been found to enhance the transcriptional activity of steroid hormone receptors. Nuclear receptor coactivator complexes, which include the vitamin-D-receptor interacting proteins (DRIPs) and thyroid receptor-associated proteins (TRAPs), enhance receptor-dependent transcription through a different mechanism. While DRIPs and TRAPs complexes interact in a ligand-dependent manner with the C-terminus of steroid receptors, they differ from other coactivators in that they lack histone acetyltransferase activity [103, 104]. Rather, DRIPs and TRAPs are thought to interact with the basal transcriptional machinery following chromatin remodeling by other coactivators such as CBP and SRC-1 [103, 104].

DRIPs coactivate ER and glucocorticoid receptor as well as thyroid hormone receptors (TR) [103]. In vitro, ERα has a similar affinity for both the DRIP205 subunit and SRC-1. DRIP205 can enhance transcription in the absence of SRC-1, as demonstrated by observations that ligand-bound vitamin D receptor incubated with nuclear extracts from

TABLE 1. Nuclear receptor coactivator expression in reproductive tissues.[a]

Coactivator	Tissue	Species	Technique	Reference	Notes
SRC-1	Mammary	Rat	ICC	[115]	
		Mouse	KO	[116]	
	Uterus	Rat	ISH	[117]	
		Sheep, cow, pig	NB	[118]	
	Ovary	Sheep, cow, pig	NB	[118]	Up-regulated by E
	Testes	Rat	NB	[119]	
	Anterior pituitary	Mouse	ISH	[120]	
		Rat	NB	[119]	Up-regulated by TH
	Brain				
	Hypothalamus	Rat	ICC, ISH, NB	[121–123]	
	Amygdala				See [122] for SRC-1a and SRC-1e expression
	Hippocampus				
	Basal ganglia				
	Isocortex				
	Cerebellum		RNP	[124]	
	Hypothalamus	Mouse	ISH	[120, 125]	
	Amygdala				
	Hippocampus				
	Olfactory bulb				
	Thalamus				
	Cerebellum				
	Cortex				
	Cerebellum	Bird	ISH	[126]	
	Telencephalon				
	Optic lobes				
	Hypothalamus				
	Preoptic area	Sheep	ICC	[127]	Expressed in GnRH neurons
SRC-2	Uterus	Rat	ISH	[117]	
		Sheep, cow, pig	NB	[118]	
	Ovary	Sheep, cow, pig	NB	[118]	Up-regulated by E
	Anterior pituitary	Rat	ISH	[122]	
	Brain				
	Cerebellum	Rat	RNP	[124]	
	Whole brain	Mouse	ISH	[116]	
	Cerebellum		ISH	[125]	
	Hippocampus				
	Hypothalamus		ISH	[128]	
SRC-3	Uterus	Rat	ISH	[117]	
		Sheep, cow, pig	NB	[118]	
	Ovary	Sheep, cow, pig	NB	[118]	Up-regulated by E
	Brain	Mouse			
	Hippocampus				
	Cerebellum				
	Olfactory bulb				
CBP/p300	Uterus	Rat	ISH	[117]	
		Sheep, cow, pig	NB	[118]	
	Ovary	Sheep, cow, pig	NB	[118]	Up-regulated by E
	Testes	Rat	NB	[119]	
	Sertoli cells		WB	[129]	
	Seminiferous tubules				
	Brain				
	Hypothalamus	Rat	WB	[121, 130]	
	Amygdala		ISH	[131]	
	Cortex				
	Hypothalamus				
	Cerebellum				
	Hippocampus		ISH, ICC	[131]	
	High vocal center	Bird	ICC	[132]	
	Robust nucleus of archistriatum				
	Area X				
	Hypothalamus				
RIP140	Uterus	Rat	ISH	[117]	
		Sheep, cow, pig	NB	[118]	
	Ovary	Sheep, cow, pig	NB	[118]	Up-regulated by E
SPA	Ovary	Sheep, cow, pig	NB	[118]	
TRAP220	Brain	Rat, mouse	ISH	[108]	
	Cerebellum				
	Pyriform cortex				
	Hippocampus				
ERAP140	Mammary gland	Human, mouse	NB	[109]	
	Uterus	Human			
	Ovary	Human			
	Testis	Mouse			
	Prostate	Human			

TABLE 1. *Continued.*

Coactivator	Tissue	Species	Technique	Reference	Notes
	Brain Hypothalamus Hippocampus Cerebellum Cortex	Human, mouse			
SRA	Placenta Brain Liver Skelatal muscle Heart	Human	NB	[111]	

[a] ICC, Immunocytochemistry; KO, knockout; ISH, in situ hybridization; NB, Northern blot analysis; RNP, RNase protection assay; WB, Western blot.

HeLa cells did not copurify SRC-1 or SRC-2 with a transcriptionally active DRIP complex [105]. Likewise, CBP was not found to interact with the DRIP complex. These findings suggest that DRIPs interact with steroid receptors as a distinct complex that does not include p160 coactivators or CBP [105].

The TRAP220 subunit has been found to interact in a ligand-dependent manner with the C-terminus of receptors, including ER and TR [106]. In coimmunoprecipitation assays, ERβ precipitated TRAP220 from cell extracts more efficiently than ERα, suggesting that TRAP220 binds preferentially to ERβ over ERα [107]. This more efficient binding of TRAP220 to ERβ than to ERα may be due to differences in the F-domain of the extreme C-terminus of these two receptors [107]. TRAP220 is expressed in a variety of neural structures during rodent embryonic development, including the neocortex, cerebellum, hippocampus, basal ganglia, and midbrain [108]. While the authors suggest that TRAP220 may function in development of brain structures [108], this intriguing possibility has yet to be investigated.

ER-associated protein 140 (ERAP140) is a recently characterized protein that interacts in a ligand-dependent manner with ERα and ERβ as well as TR and retinoic acid receptor [109]. Interestingly, ERAP140 differs from other coactivators in that it does not contain an NR box LXXLL motif but rather interacts with liganded ER through a domain located between amino acids 489 and 559 of ERAP140. In addition, this coactivator does not have any sequence homology with any other known coactivators, suggesting that it represents a novel class of nuclear receptor coactivators [109]. The expression of ERAP140 is tissue specific, with high expression in mammary gland, ovaries, uterus, testes, and prostate [109]. Interestingly, highest expression of this coactivator was found in brain, including behaviorally relevant areas, such as the hypothalamus [109]. However, the function of this novel coactivator in reproductive function has not yet been investigated.

Steroid receptor RNA activator (SRA) is a unique coactivator in that it functions as an RNA transcript to enhance transcriptional activation of steroid receptors [110, 111]. SRA was found to increase transactivation of a variety of nuclear hormone receptors, including ER, PR, GR, AR, and TR, in a ligand-dependent manner. As mentioned previously, coactivators can reverse squelching of one nuclear receptor by another. While liganded ER reduced PR transcriptional activation by 50%, addition of SRA reversed this squelching effect of ER [111]. The necessity of SRA for efficient PR transactivation is further demonstrated by a 70% reduction in PR target gene expression in HeLa cells by cotransfection of SRA antisense oligonucleotides [111]. In cells that were treated with SRC-1 and SRA antisense ODNs, ERα activity was decreased by 70% compared to that of control-treated cells [110]. Antisense to either SRA or SRC-1 alone had a less dramatic effect on ERα activity, suggesting SRA association with SRC-1 [110]. In further support of this association, SRA was found to copurify with SRC-1 [111]. Taken together, these findings further support the association of SRA and SRC-1 in a coactivator complex necessary for full steroid receptor transcriptional activity. While it is unclear whether this coactivator mediates reproductive function, SRA provides a novel mechanism of steroid receptor transactivation by functioning as an RNA complex to confer specificity of protein complexes recruited by liganded receptors.

NUCLEAR RECEPTOR COACTIVATORS IN REPRODUCTION

Development of Reproductive Behavior

Nuclear receptor coactivators are expressed in a variety of tissues as shown in Table 1. Many of the nuclear receptor coactivators appear to be expressed in a tissue-specific manner and are regulated by hormones. Gonadal hormones are critical for the expression of reproductive behaviors in adult rodents. High levels of T on the day of birth masculinize and defeminize adult sexual behaviors in rodents [8, 9]. However, as discussed previously, many of the physiological actions of T are due to aromatization of T to E. Estradiol treatment of males during the first 10 days of life led to increased frequency of intromissions and ejaculation in T-treated adult castrates compared to males treated neonatally with T [13, 112]. Interestingly, females treated with T during the prenatal and neonatal period and T in adulthood will display masculine copulatory behaviors (e.g., mounting) and fewer feminine behaviors than normal females [113, 114].

Recently, nuclear receptor coactivators, such as SRC-1 and CBP, have been found to profoundly affect hormone-dependent sexual differentiation of the brain and adult sexual behaviors [123, 130]. Auger and colleagues investigated the role of SRC-1 in hormone-dependent sexual differentiation of the SDN [123]. 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, T 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. 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 [123]. Males were castrated in adulthood and following T

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. Interestingly, male sexual behavior in these animals did not differ. 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 [123].

CBP is expressed in reproductively relevant brain areas in a dimorphic manner and functions in the development of masculine sexual behavior [130]. On the day of birth, males express 53% more CBP-immunoreactive (CBP-IR) cells in the mPOA, and 83% more CBP-IR cells in the VMN, than females. 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, T-treated females that received CBP antisense in the hypothalamus on PN0–2 displayed higher levels of lordosis than androgenized females treated with control ODNs [130]. However, CBP antisense treatment did not affect development of male sexual behavior in these androgenized females. Taken together with the previous study, it appears that both SRC-1 and CBP are necessary for the defeminizing actions of ER but not the masculinizing actions of AR during early development.

Nuclear Receptor Coactivators in Neural Gene Expression and Female Sexual Behavior

Our lab and others have investigated the role of nuclear receptor coactivators in hormone-dependent gene expression in brain and behavior in adults [121, 128]. E-induction of PR gene expression in the VMN is necessary for hormone-dependent female sexual behavior [46]. Using double label-fluorescent immunocytochemistry, studies from our lab reveal that most E-induced PR-containing neurons in the VMN express CBP, while more than 50% express SRC-1 [86]. Therefore, we tested the hypothesis that SRC-1 and CBP are critical in modulating ER-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 [121]. Our findings are supported by previous in vitro studies indicating that SRC-1 and CBP function together to modulate ER activity [91]. 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 [133]. A similar study in brain has confirmed our findings that SRC-1 is necessary for E-induction of PR expression in the VMN [128]. These findings were extended by demonstrating that antisense to SRC-2 reduced PR expression in this nucleus, suggesting that SRC-2 also functions in the full expression of E-induced PR in brain.

Given that nuclear receptor coactivators are critical for hormone-dependent gene expression in brain, we next tested the hypothesis that these coactivators function in the expression of hormone-dependent behaviors. Female rats were bilaterally infused with either antisense ODNs to both SRC-1 and CBP mRNA or scrambled control ODNs into the VMN for three consecutive days. On Days 2 and 4, rats were treated with E and P, respectively. Four hours after P, rats were tested for receptive behavior with an experienced male rat. Infusion of antisense to SRC-1, and CBP mRNA decreased the display of sexual receptivity. These findings were confirmed by another study showing that SRC-1, and also SRC-2, influence the expression of lordosis in hormone-primed females [128]. Thus, reduction of nuclear receptor coactivators in brain reduces the expression of female sexual behavior, further supporting a role of coactivators in hormone-dependent actions in brain. We are currently investigating the function of nuclear receptor coactivators in the modulation of PR activity in brain and behavior.

Nuclear Receptor Coactivators in Peripheral Reproductive Tissues

While a variety of in vivo studies have elucidated the function of nuclear receptor coactivators in brain as discussed previously, we are now starting to learn more about their function in peripheral reproductive tissues. Many nuclear receptor coactivators are found in a variety of peripheral tissues and across different species (see Table 1). SRC-1 null mutant mice, while fertile, exhibit decreased growth of steroid-responsive tissues, such as the uterus, prostate, and testes, compared to wild-type mice [116]. Interestingly, TIF2 (SRC-2) was up-regulated in tissues such as the brain and testes, suggesting that increased expression of this coactivator may compensate for the absence of SRC-1 [116]. Nevertheless, these studies indicate that SRC-1 is necessary for E and T action in peripheral reproductive tissues.

SRC-3 knockouts have a variety of deficits in the development of steroid-sensitive reproductive tissues [89]. In female SRC-3 KOs, puberty is delayed 3 days compared to wild-type mice. However, treatment with E can alleviate this delay, suggesting that later puberty in these animals is due to problems with E synthesis. Furthermore, although these SRC-3 KO mice are fertile, they ovulate fewer eggs, are less likely to become pregnant, and deliver fewer pups than wild-type mice or heterozygous SRC-3 null mice. Estrous cycles in SRC-3 KOs were nearly twice as long as cycles in wild-type mice. The authors suggest that the disrupted reproductive function in these mice may be due to defects of the ovary. Furthermore, lack of SRC-3 in oocytes may result in decreased oocyte development, leading to subfertility in knockout mice.

Studies over the past decade have dramatically increased our knowledge of steroid hormone action in reproduction and in particular steroid-mediated gene expression in reproductive tissues. The mechanisms by which steroids act in a tissue-specific manner is a fundamental issue in steroid hormone action. Nuclear receptor coactivators appear to be critical in the fine-tuning of steroid responsiveness within individual cells in the brain and reproductive tissues. However, the function of many of these coactivators in reproductive physiology and behavior is not clearly understood. In order to better understand the basic mechanisms of reproductive function, it is essential to investigate further the role of nuclear receptor coactivators in modulating hormone action in steroid-responsive reproductive tissues. Future studies of these important nuclear receptor coactivators in steroid action will greatly enhance our knowledge of hormone-regulated reproductive behavior and physiology.

NOTE ADDED IN PROOF

The following references are to be added to the SRC-1 section of Table 1:

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