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Mechanisms and significance of nuclear receptor auto- and cross-regulation

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Abstract

The number of functional hormone receptors expressed by a cell in large part determines its responsiveness to the hormonal signal. The regulation of hormone receptor gene expression is therefore a central component of hormone action. Vertebrate steroid and thyroid hormones act by binding to nuclear receptors (NR) that function as ligand-activated transcription factors. Nuclear receptor genes are regulated by diverse and interacting intracellular signaling pathways. Nuclear receptor ligands can regulate the expression of the gene for the NR that mediates the hormone's action (autoregulation), thus influencing how a cell responds to the hormone. Autoregulation can be either positive or negative, the hormone increasing or decreasing, respectively, the expression of its own NR. Positive autoregulation (autoinduction) is often observed during postembryonic development, and during the ovarian cycle, where it enhances cellular sensitivity to the hormonal signal to drive the developmental process. By contrast, negative autoregulation (autorepression) may become important in the juvenile and adult for homeostatic negative feedback responses. In addition to autoregulation, a NR can influence the expression other types of NRs (cross-regulation), thus modifying how a cell responds to a different hormone. Cross-regulation by NRs is an important means to temporally coordinate cell responses to a subsequent (different) hormonal signal, or to allow for crosstalk between hormone signaling pathways.

I. Introduction

Steroid and thyroid hormones play central roles in animal development, physiology and behavior. The classical mode of signaling for these hormones is through binding to their cognate nuclear receptors (NRs), which are ligand-activated transcription factors that regulate the transcription of a subset of genes expressed by a cell. Nuclear receptors that mediate the actions of classical hormones can be divided into two groups based on their evolutionary relatedness, subcellular localization and mode of action (Germain et al., 2006). The type I NRs include the steroid hormone receptors: androgen – AR; estrogen – ER; glucocorticoid – GR; mineralocorticoid – MR; and progesterone receptor - PR. In the unliganded state, type I NRs are located in the cytoplasm associated with molecular

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chaperones (heat shock proteins) that maintain the receptors in a conformation that allows for ligand binding but not DNA binding. Upon hormone binding, type I NRs undergo a conformational change that results in the release of components of the chaperone complex, exposure of a nuclear localization sequence, and translocation to the nucleus where they associate with chromatin and regulate gene transcription. Both DNA binding-dependent (at hormone response elements - HREs) and DNA binding-independent actions of type I NRs have been described (Mangelsdorf et al., 1995; Reichardt et al., 1998).

The type II NRs include thyroid hormone (TR), Vitamin D (VDR), retinoic acid (RAR) and retinoid X (RXR) receptors. In contrast to the type I NRs, the type II NRs reside in the nucleus constitutively bound to DNA, and usually act as transcriptional repressors in the absence of hormone (e.g. TRs; Aranda and Pascual, 2001; Ribeiro et al., 1995). Both type I and type II NRs control gene transcription by recruiting proteins that cause chromatin remodeling, or posttranslational modification to histones that promote a relaxed or repressive chromatin structure (Robyr et al., 2000). Steroid and thyroid hormones also act via plasma membrane-associated receptors (Furuya et al., 2009; Kampa and Castanas, 2006; Levin, 2009; Tasker et al., 2006; Thomas, 2008; Zhu et al., 2008). The types of proteins responsible for transducing steroid and thyroid hormone (TH) actions at the plasma membrane include classical membrane-resident proteins such as G protein-coupled receptors and ligand-activated ion channels; but, there is also evidence for NRs associating with the plasma membrane and signaling via intracellular kinases. Furthermore, there may be crosstalk between plasma membrane (nongenomic) and nuclear (genomic) signaling pathways. Here we focus largely on the genomic signaling pathways initiated by binding of a hormone to its cognate NR in the cytosol or nucleus to influence NR gene expression.

Since their discovery there has been great interest in delineating the molecular mechanisms by which NRs regulate target gene expression owing to their central roles in development, metabolism and behavior. Comparatively less attention has been paid to the physiological and molecular mechanisms by which the expression of NR genes is regulated. The number of functional receptors expressed by a cell determines its hormone responsiveness, and the expression of NRs may change with stage of development, physiological or pathological state. For these reasons, knowledge of the mechanisms by which NR gene expression is controlled is critical for understanding hormone action. This review focuses on two aspects of the regulation of NR gene expression. First, we discuss the molecular mechanisms and physiological significance of NR autoregulation, the regulation of the expression of a NR by its ligand. We then discuss NR cross-regulation, the regulation of the expression of one NR gene by a different type of NR. In each case, the amount of functional NR in a cell is regulated, but the mechanisms by which this occurs may be transcriptional or posttranscriptional, or both. Where data are available we attempt to describe these regulatory mechanisms, and we also discuss the physiological significance of changes in NR expression. The focus of this review is on vertebrate NRs; however, similar phenomena have been described in invertebrates. For example, the ecdysone receptor is autoinduced during insect metamorphosis (Riddiford et al., 2001; Thummel, 1995). Auto- and cross-regulation of NRs is an ancient and evolutionarily conserved regulatory mechanism for controlling cell responses to hormones.

II. Nuclear Receptor Autoregulation

The regulation of the expression of a NR gene by its hormone-bound protein product is an important means for modulating hormone action in developing animals, within the reproductive system of adult animals, and for maintaining homeostasis. Autoregulation of NR genes can be positive (autoinduction; i.e., homologous upregulation) or negative (autorepression; homologous down-regulation). Autoinduction leads to the biosynthesis of

more NRs by the cell, thus enhancing cellular responsiveness to the hormone. Autorepression is a homeostatic mechanism to modulate hormone action by downregulating the receptor for the hormone.

There are several mechanisms by which NR expression may be autoregulated that can be broadly described as transcriptional or posttranscriptional (Fig. 1). At the transcriptional level, regulation can be either direct, where the ligand-bound NR associates with its own gene to positively or negatively regulate transcription, or indirect, where the NR induces expression of a transcription factor(s) that regulates transcription of the NR gene (Fig. 1A,B). Both direct and indirect regulation may also occur, where the NR binds to and regulates expression of its own gene, but full transcriptional regulatory activity depends on the induction of a transcription factor(s) that regulates transcription of the NR gene (cooperative regulation; Fig. 1C). At the posttranscriptional level, the NR may induce expression of genes that influence mRNA stability or protein stability (Fig 1D,E,F; or perhaps also protein translation or protein bioactivity through posttranslational modifications).

Under physiological conditions, NR autoinduction is often observed when positive feedback within the neuroendocrine system increases hormone production, leading to a progressive rise in plasma hormone concentrations. Within hormone target tissues, NR autoinduction generates a feed-forward response that ends when the positive feedback on hormone production is terminated. For example, during the mammalian ovarian cycle gonadotropins secreted by the pituitary gland stimulate estrogen production by the ovarian follicle, and rising plasma estrogen concentration causes positive feedback on the hypothalamo-pituitary axis. During the mid- to late follicular phase, when plasma estrogen titers increase, estrogen stimulates proliferation of uterine endometrial cells; estrogen action may be facilitated by the autoinduction of the ER in these cells, a feed-forward response. These actions are terminated, and plasma estrogen concentration drops upon ovulation induced by the surge in plasma luteinizing hormone caused by the positive feedback signal of estrogen. Nuclear receptor autoinduction is also seen during animal development where it serves as a feed-forward mechanism to drive the developmental process. The most studied example of this phenomenon is amphibian metamorphosis, where rising plasma TH titers cause autoinduction of TRs in target tissues (Tata, 2000).

Nuclear receptor autorepression may function as a component of negative autoregulatory feedback loops to maintain homeostasis. For example, the GR is expressed in the brain in limbic structures involved with fear and anxiety (amygdala, bed nucleus of the stria terminalis), and learning and memory (hippocampus), and in neurosecretory neurons that regulate the hypothalamo-pituitary-adrenal (HPA) axis. The GR plays a central role in mediating negative feedback on the HPA axis, but also may facilitate stress-related behaviors through feed-forward actions on limbic structures. A physiological means to limit negative feedback of glucocorticoids on the HPA axis once the system has returned to baseline, and to 'reign-in' the facilitating effects of glucocorticoids on fear and anxiety is to downregulate GR expression in the hypothalamus and limbic structures, respectively.

A. Type I Nuclear Receptors

Sex steroids (estrogens, androgens and progestins) control the development of the male and female urogenital tracts and secondary sex characteristics, sexual behavior and gametogenesis. Corticosteroids (glucocorticoids and mineralocorticoids) control developmental, physiological and behavioral responses to stress and regulate hydromineral balance and blood pressure. Vitamin D regulates plasma calcium and phosphorous homeostasis, and skeletal mineralization and remodeling.

1. Estrogen Receptor (ER)—All jawed vertebrates that have been studied to date have two ER subtypes, designated ER α and ER β (Escriva et al., 2004; Germain et al., 2006); some bony fishes have additional paralogs. Estrogen receptor expression is regulated by estrogens, most commonly through autoinduction. The molecular mechanisms that have been identified involve direct transcriptional regulation of ER genes by the ER and modulation of ER mRNA stability. ER autoinduction appears to be important for estrogen action on the female reproductive tract.

Autoinduction: One of the earliest reports of NR autoinduction was the demonstration that estrogen injection increased ER in liver cell nuclei of male frogs (*Xenopus laevis*; Westley and Knowland, 1979). Vitellogenin (Vtg) is a yolk protein synthesized by the female liver in nonmammalian species, and Vtg synthesis and deposition in eggs occurs over weeks to months, a process called vitellogenesis. The synthesis of Vtg is regulated by estrogen, and although males normally do not synthesize Vtg (and have very low ER levels in liver cells), it can be induced by estrogen injection. If male frogs are given a second injection of estrogen several weeks after the synthesis of Vtg caused by the initial injection has waned, the kinetics of Vtg production is significantly faster than that of the initial injection (Clemens, 1974). This led Westley and Knowland (1979) to hypothesize, and to confirm, that the primary estrogen injection caused the synthesis of ERs that then sensitized cells to a second exposure to the hormone. Subsequent studies confirmed and extended these findings in the frog (Barton and Shapiro, 1988; Shapiro et al., 1989; Varriale and Tata, 1990). Indeed, a single injection of estrogen into male *X. laevis* caused a robust (18 fold) and prolonged elevation of liver ER mRNA that persisted at the same level for the 125 day duration of the experiment (Barton and Shapiro, 1988). Autoinduction of ER, and a parallel increase in vitellogenin mRNA was also reported to occur in liver of several fish species (Bowman et al., 2002; Marlatt et al., 2008; Pakdel et al., 1991; Yadetie et al., 1999).

In addition to the liver, ER autoinduction was reported in frog oviduct cells (Varriale and Tata, 1990), mouse uterus (Bergman et al., 1992; Kamiya et al., 1996; Nephew et al., 2000; Yamashita et al., 1990) and rat pituitary gland (Friend et al., 1995). Estrogen also causes ER autoinduction in testis and prostate of male rodents (Prins, 1992; Prins and Birch, 1997; Sato et al., 1994; Tena-Sempere et al., 2000) where neonatal exposure to high doses of estrogen caused atrophy of the testes, suppressed prostate growth and reduced responsiveness to androgen (Brown-Grant et al., 1975; Naslund and Coffey, 1986; Prins and Korach, 2008; Rajfer and Coffey, 1978).

Autorepression: In the mammary gland the ER is negatively regulated by estrogen. Treatment with estrogen decreased ER mRNA levels in the estrogen-sensitive human breast cancer cell line MCF-7 (Berkenstam et al., 1989; Read et al., 1989). Injections of estrogen into lactating mice decreased ER mRNA in the mammary gland; the reduction in ER expression may be important for the normal transition from lactation to the postlactational phase (Hatsumi and Yamamuro, 2006).

Molecular mechanisms of ER autoregulation: Transcriptional activation of ER genes by estrogen via identified estrogen response elements (EREs) has been shown in fish, frog and mammal cells. Estrogen activated ER gene transcription in the breast cancer cell line MCF7 as measured by nuclear run-on assay (Saceda et al., 1988). Treilleux et al. (1997) identified three half estrogen response elements (EREs) upstream of the transcription start site of the human ER gene that supported estrogen induction in MCF7 cells. In the frog ER gene a functional ERE was identified about 480 bp upstream of the transcription start site within the protein coding region (Lee et al., 1995). The rainbow trout ER gene is regulated by an ERE located in the proximal promoter region of the gene (Le Drean et al., 1995; Petit et al., 1999).

Estrogen has also been shown to stabilize ER mRNAs in fish liver at the onset of vitellogenesis (Flouriot et al., 1996), and in mammalian (sheep) uterus at the time of the preovulatory estrogen surge (Ing and O'Malley, 1995; Ing, 2005; Ing et al., 2008; Ing and Ott, 1999; Mitchell and Ing, 2003). These actions of estrogen were likely mediated by the ER, since they could be blocked by estrogen receptor antagonists.

The molecular mechanisms by which the ER is negatively regulated by its ligand are poorly understood. Hatsumi and Yamamuro (2006) showed that in mouse mammary gland estrogen injection decreased phosphorylation of the signal transducer and activator of transcription 5, a known transcriptional regulator of the ER gene (Hatsumi and Yamamuro, 2006). However, the doses of estrogen used in this study were supraphysiological, and it is therefore uncertain whether the findings are of physiological relevance.

Physiological significance of ER autoinduction: Estrogen receptor autoinduction may be necessary for cells to achieve maximal response to the hormonal signal. Studies in frog hepatocytes and oviductal cells showed a close association between ER number in cell nuclei and the rate of *de novo* transcription of ER target genes (vitellogenin and FOSP-1 genes) (Perlman et al., 1984; Varriale and Tata, 1990). Inhibition of protein synthesis that blocked the estrogen-induced increase in ER protein, or co-treatment with ER antagonists reduced estrogen-dependent accumulation of vitellogenin and FOSP-1 mRNAs, suggesting that ER target gene activation depends on the level of ER in the cell. Vitellogenin synthesis becomes responsive to estrogen at metamorphic climax in *X. laevis* tadpoles (Huber et al., 1979; Knowland, 1978; May and Knowland, 1980), which corresponds to the developmental stage when the ER can be autoinduced (May and Knowland, 1981; Rabelo et al., 1994). This suggests that the increase in Vtg biosynthesis is causally linked to the increase in ER. In mammals, estrogen is known to increase proliferation of epithelial and stromal cells of the uterine endometrium, coincident with ER autoinduction (Kamiya et al., 1996; Nephew et al., 2000; Yamashita et al., 1990).

2. Androgen Receptor (AR)—Autoregulation of the AR has been reported in virtually every cell type that expresses the gene. This regulation is predominantly negative, although there are some examples where androgens cause autoinduction of the AR. The regulation of AR mRNA and protein is complex, occurring at both transcriptional and posttranscriptional levels.

Autoinduction: The AR is autoinduced in specific regions of the prostate gland (Takeda et al., 1991; although, the AR is negatively autoregulated in other regions of the gland – discussed below), other organs of the male urogenital tract and in tissues displaying male secondary sex characteristics. For example, testosterone induced AR mRNA in rat penile smooth muscle cells (Gonzalez-Cadavid et al., 1993) and in hamster harderian gland, a tubulo-alveolar gland found in the orbital activity (Dominguez et al., 1994; Varriale, 1996). Evidence for positive regulation of AR mRNA by androgens has also been shown for lizard and bird testis (Cardone et al., 1998; Nastiuk and Clayton, 1994). In the frog *Rana esculenta*, testosterone treatment increased AR mRNA in the harderian gland and thumb pad (Varriale and Serino, 1994).

Androgen receptor may also be autoinduced in non-reproductive organs. Treatment of human osteoblast cell lines with androgen increased AR mRNA in a time and dose-dependent manner that was blocked by cotreatment with the antiandrogen flutamide (Takeuchi et al., 1994; Wiren et al., 1997). Indirect evidence for AR autoinduction in rat hippocampus was suggested by the findings that castration, or injection of AR antagonist in gonad-intact males caused a reduction in AR mRNA levels (Kerr et al., 1995).

Autorepression: By contrast to AR autoinduction, the AR appears to be autorepressed in most tissues in which the gene is expressed. For example, castration of male rats increased, while testosterone replacement decreased AR mRNA levels in the anterior prostate gland, epididymis, kidney and brain (Prins and Woodham, 1995; Quarmby et al., 1990). Negative AR mRNA autoregulation was also observed in the human prostate cancer line LNCaP (Blok et al., 1992; Wolf et al., 1993) and in breast cancer cell lines T47D and MFM-223 (Hackenberg et al., 1992; Wolf et al., 1993).

Molecular mechanisms of AR autoregulation: Direct transcriptional regulation of the human AR gene by AR protein is supported by the discovery of several putative androgen response elements (AREs) located within a 350 bp stretch of the AR coding region (Dai and Burnstein, 1996; Grad et al., 1999). This DNA sequence conferred androgen-dependent activation to a minimal promoter-reporter construct in transfection assays of prostatic PC3 cells, and electrophoretic mobility shift assays and DNase I footprinting showed that the AR can bind to this region (Dai and Burnstein, 1996; Grad et al., 1999). In addition, Wren et al. (1997) found that a 2.9 kb fragment of the 5' flanking region of the human AR gene (-2330 to +572) conferred positive androgen regulation on a chloramphenicol acetyltransferase reporter construct transfected into osteoblast cells. These investigators did not define the specific sequences within this region of the human AR gene responsible for androgen regulation. Promoter analysis of the AR gene in hamsters identified an androgen/glucocorticoid response element located 473 bp upstream of the transcription start site, and this region was shown to associate with AR in gel shift assays (Varriale and Esposito, 2005). Whether a homologous DNA element is present in the human AR gene has not been reported. Taken together, the findings suggest that there may be multiple AREs present in mammalian AR genes that mediate autoinduction. The molecular basis for autorepression of the AR gene is not well understood, but thought to occur independent of the exonic AREs that are proposed to function in AR autoinduction (Burnstein, 2005).

Physiological significance of AR autoinduction: The development of secondary sex characteristics in males depends on circulating androgens. There are distinct sex differences in AR expression that may depend on androgen action, and the level of AR expressed in a tissue likely determines the physiological and morphological effects that androgens have on that tissue. For example, in hamsters, sexual dimorphism of the harderian gland is attributed to the different circulating levels of androgen between sexes (Payne, 1994). Both male and female hamster harderian glands express AR, but receptor levels are thirty times higher in male than in female, suggesting that the expression level of AR is in part responsible for the sex-associated phenotypic differences in the gland (Dominguez et al., 1994). A similar sex difference in AR expression was observed in hamster facial motor neurons where females express 50% less AR mRNA compared to males (Drengler et al., 1996). In this study, they showed that gonadectomy decreased AR mRNA in males but not in females, and replacement of testosterone increased AR mRNA in males. The sex-dependent difference in AR autoinduction may be a mechanism for testosterone to augment androgen responsiveness of facial nerve regeneration in males compared with females (Jones, 1993).

At the cellular level, studies in cell lines derived from rat prostate tumor or hamster ductus deferens smooth muscle showed that androgen treatment promoted cell proliferation, and the proliferative response correlated with an increase in the number of functional ARs in the cells (Syms et al., 1985; Syms et al., 1983a; Syms et al., 1983b). The upregulation of AR mRNA in osteoblast and prostate cancer cells has been associated with sensitization to androgens (Burnstein, 2005).

3. Progesterone Receptor (PR)—Unlike the ER and AR that show both autoinduction and autorepression, the PR appears to be exclusively negatively regulated by its ligand.

Autorepression of PR has been shown in guinea pig and rabbit uterus (Isomaa et al., 1979; Milgrom et al., 1973), rat and guinea pig brain (Blaustein and Turcotte, 1990; Parsons et al., 1981), chicken oviduct (Mester and Baulieu, 1977; Syvala et al., 1998) and in human breast cancer cell lines (Alexander et al., 1989; Mullick and Katzenellenbogen, 1986; Nardulli and Katzenellenbogen, 1988; Read et al., 1988).

The progesterone-mediated decrease in PR expression may occur at both transcriptional and posttranscriptional levels, where progesterone decreases PR mRNA (Alexander et al., 1989; Read et al., 1988; Savouret et al., 1991; Savouret et al., 1994a) and promotes PR turnover (Blaustein and Turcotte, 1990; Isomaa et al., 1979; Mester and Baulieu, 1977; Mullick and Katzenellenbogen, 1986; Read et al., 1988). The reduction in PR mRNA level is accompanied by a parallel decrease in receptor binding activity (Blaustein and Turcotte, 1990; Parsons et al., 1981). DNase I footprinting assay identified several binding sites for the PR located in the 5' flanking region, and binding sites for the ER in the 5' flanking region and near the translation initiation site of the rabbit PR gene. The PR gene is positively regulated by the ER (discussed in greater detail below), and both transactivation by the ER, and transrepression by the PR are mediated by intragenic sequences surrounding the translation initiation site that correspond to the identified ERE, but not by the putative hormone response elements in the 5' flanking region of the gene (Savouret et al., 1991). Although repression by progestins was mediated by the region containing the ERE, the PR did not bind to this element (Savouret et al., 1994b). The mechanism for PR autorepression may involve antagonism of estrogen-dependent induction of the PR gene through protein-protein interactions with the ER (Savouret et al., 1994b).

In addition to negative regulation of PR gene transcription, progestins can also reduce the level of PR protein in the cell through alterations in PR turnover. For example, in chicken oviduct, progesterone causes the PR to become ubiquitinated, which targets the receptor to the proteasomal pathway for degradation (Syvala et al., 1998).

4. Corticosteroid Receptors (GR and MR)—Vertebrates have two corticosteroid receptors, the MR (type I) and the GR (type II). Both autoinduction and autorepression have been shown for both receptors, although autorepression appears to be more common. Of the two receptors the GR has been better studied.

Autoinduction: Autoinduction of GR was demonstrated in human leukemic T cells (CEM C7 and 6TG1.1) that exhibit glucocorticoid-dependent cell lysis (Denton et al., 1993; Eisen et al., 1988; Ramdas et al., 1999; Thompson et al., 1992). In these cells, the glucocorticoid-induced increase in GR mRNA preceded apoptosis, and was therefore not a consequence of cell lysis (Eisen et al., 1988). GR autoinduction was resistant to protein synthesis inhibition, and was completely blocked by the GR antagonist RU486, suggesting that GR autoinduction in these cells is directly mediated by the GR (Denton et al., 1993). Autoinduction of GR was also reported in tadpole intestine (Krain and Denver, 2004).

Autorepression: Downregulation of GR expression by glucocorticoids has been described in mammals and in frogs, and may be a more common form of autoregulation of the GR than autoinduction. The GR plays a central role in mediating negative feedback by glucocorticoids on the activity of the hypothalamic-pituitary-adrenal (HPA) axis (reviewed by De Kloet et al., 1998). It is expressed in the hypothalamus and limbic structures (e.g., amygdala, bed nucleus of the stria terminalis, hippocampus) of the brain, and in the anterior pituitary gland where it participates in negative feedback by glucocorticoids on corticotropin-releasing factor (CRF) and adrenocorticotrophic hormone (ACTH; reviewed by Denver, 2009b; Yao et al., 2008). Glucocorticoid receptor expressed in these tissues is predominantly negatively regulated by glucocorticoids. For example, administration of

glucocorticoids decreased GR protein and/or mRNA throughout the brain of rats and frogs (Chao et al., 1998; Ghosh et al., 2000; Han et al., 2007; Holmes et al., 1995; Hugin-Flores et al., 2004; Reul et al., 1989b; Sapolsky et al., 1984; Spencer et al., 2000; Yao et al., 2008). In rats, adrenalectomy increased GR protein in the hippocampus, hypothalamus, and cortex (Kalman and Spencer, 2002; O'donnell et al., 1995; Spencer et al., 2000) and GR mRNA in the hippocampus; the latter could be reversed by supplementation with glucocorticoids (Chao et al., 1998; Han et al., 2007; Holmes et al., 1995; Hugin-Flores et al., 2004; Okret et al., 1991; Reul et al., 1989b; Tornello et al., 1982).

Autorepression of the GR by circulating glucocorticoids may be an important mechanism for regulating the responsiveness of the HPA axis during chronic stress. For example, rats exposed to repeated or chronic stressors had reduced GR mRNA expression in hypothalamic and limbic structures involved in regulating the HPA axis (Gomez et al., 1996; Herman and Watson, 1995; Makino et al., 2002; Makino et al., 1995; Nishimura et al., 2004; Sapolsky et al., 1984). The GR also appears to be negatively regulated by corticosteroids in other cell types; e.g., lymphocytes, liver, lung and pancreatic acinar cells (Dong et al., 1988; Okret et al., 1991; Okret et al., 1986; Rosewicz et al., 1988).

In contrast to the GR, which shows both forms of autoregulation, only autorepression has been reported for the MR. In the rat kidney, adrenalectomy increased MR mRNA (Kalinyak et al., 1992) and receptor binding (Claire et al., 1981; Stephenson and Funder, 1987). In rodent brain, the GR is widely expressed compared to the MR, whose expression is largely restricted to the hippocampus (Chao et al., 1989). Similar to kidney, adrenalectomy elevated MR mRNA (Chao et al., 1998; Herman et al., 1989; Kwak et al., 1993; Patchev et al., 1994; Reul et al., 1989a) and protein levels (Chao et al., 1989; Kalman and Spencer, 2002; Stephenson and Funder, 1987) in the hippocampus. Both acute and chronic stress caused downregulation of MR mRNA in the hippocampus (Fujikawa et al., 2000; Herman and Watson, 1995; Lopez et al., 1998). Use of specific agonists for the GR or MR showed that MR downregulation was mediated by the MR (Chao et al., 1998).

Molecular mechanisms of GR and MR autoregulation: Several molecular and cellular mechanisms have been proposed to explain the downregulation of GR expression by glucocorticoids. These include 1) the inhibition of GR gene transcription (Dong et al., 1988; Okret et al., 1991; Rosewicz et al., 1988), 2) posttranscriptional regulation (e.g., decreased mRNA stability or translatability; Burnstein et al., 1991; Meyer and Schmidt, 1995; Okret et al., 1986; Vedeckis et al., 1989), and 3) posttranslational regulation (e.g., decreased protein stability and/or increased protein degradation; Dong et al., 1988; Okret et al., 1991; Webster et al., 1997).

Glucocorticoid administration decreased the rate of transcription of the GR gene, as measured by nuclear run on assay, and this was independent of protein synthesis, suggesting that the GR gene is directly regulated by the GR (Dong et al., 1988; Okret et al., 1991; Okret et al., 1986; Rosewicz et al., 1988). In further support of this hypothesis, GR was found to associate with the coding and 3' untranslated regions of the GR gene by immunoprecipitation and DNase I footprinting assays (Burnstein et al., 1990; Okret et al., 1986). Deletion of a 1 kb fragment within the human GR coding region abolished negative GR autoregulation, suggesting that there are intragenic sequences responsible for autorepression (Burnstein et al., 1990). The decrease in GR mRNA was paralleled by a decrease in GR protein levels, which could be due to decreased transcription and increased GR protein turnover or both (Dong et al., 1988; Yao et al., 2008). Upon hormone binding the GR translocates to the nucleus where it binds DNA to regulate gene transcription. It is subsequently degraded through a proteasome-mediated mechanism (Conway-Campbell et al., 2007; Deroo et al., 2002). Although the molecular mechanism for MR autorepression is

not known, there is evidence that it can occur at the level of gene transcription (Herman and Watson, 1995).

Physiological significance of GR autoinduction: Support for the biological significance of GR autoinduction in glucocorticoid-induced cell death was provided by Ramdas et al. (1999) where they were able to rescue the apoptotic effects of glucocorticoids in a cell line expressing mutant GR by expressing varying levels of wild type GR. They transfected a wild type human GR expression plasmid into ICR27TK.3 cells, a cell line derived from the human leukemic cell line 6TG1.1 that expresses an activation deficient mutant human GR. They found that basal levels of GR expression in human leukemic T cells had minimal effect on cell growth and cell death, while overexpression of GR to levels similar to those seen after GR autoinduction resulted in growth arrest and apoptosis. These findings suggest that basal levels of GR are not sufficient to elicit an apoptotic response, and that GR autoinduction may provide a means to amplify the hormone signal needed for cell death in response to steroid treatment (Ramdas et al., 1999).

B. Type II Nuclear Receptors

1. Retinoic Acid Receptor (RAR)—Retinoic acid receptors play important roles in mediating the actions of retinoic acid on cell differentiation and proliferation during vertebrate development. There are three RAR receptor subtypes (RAR α , β , γ) encoded by three separate genes (Benbrook et al., 1988; Brand et al., 1988; Giguere et al., 1987; Krust et al., 1989; Petkovich et al., 1987; Zelent et al., 1989). Of the three subtypes, both human and rodent RAR β have been found to be positively regulated by retinoic acid in several tissues (liver, liver, testes; de The et al., 1989; de The et al., 1990; Haq et al., 1991). Autoinduction of RAR β occurred at the level of transcription as evidenced by nuclear run on assays and treatment with inhibitors of RNA and protein synthesis (de The et al., 1989). Deletion mapping of the human RAR β promoter identified a region immediately upstream of the transcription start site that contained a functional retinoic acid responsive element (RARE; de The et al., 1990); an identical, functional RARE was identified in the homologous region of the mouse gene (Sucov et al., 1990). The mouse RAR α (the RAR α 2 isoform) was also found to be autoinduced in a mouse embryonic carcinoma cell line although not as strongly as RAR β (Leroy et al., 1991b). The autoregulation of RAR α 2 was attributed to the presence of a functional RARE located in the RAR α proximal promoter that closely resembles the RARE in the RAR β promoter (Leroy et al., 1991a).

2. Vitamin D Receptor (VDR)—The vitamin D receptor mediates the actions of 1,25-dihydroxyvitamin D₃ (vitamin D₃) on calcium homeostasis. Autoregulation of the VDR plays an important role in the actions of vitamin D₃, and so far, only positive regulation has been reported. For example, autoinduction of the VDR has been reported in several cell lines (Mahonen and Maenpaa, 1994; McDonnell et al., 1987; Pan et al., 1991). In animals, autoregulation of the VDR is tissue-specific; for example, vitamin D₃ increases VDR mRNA levels in the kidney (Healy et al., 2005; Healy et al., 2003), parathyroid gland (Naveh-Many et al., 1990) and skin (Zineb et al., 1998), but not in the intestine (Wiese et al., 1992; Zineb et al., 1998; but see Strom et al., 1989). Autoinduction of VDR in the kidney depends on a normal serum calcium level (Healy et al., 2005; Healy et al., 2003). Vitamin D₃ causes upregulation of VDR mRNA in cultured osteoblastic cells, which suggests that the gene can be autoinduced in bone (Mahonen and Maenpaa, 1994; Zella et al., 2006; Zella et al., 2010).

Vitamin D receptor autoinduction involves both transcriptional and posttranscriptional mechanisms. Earlier studies found that vitamin D₃ stabilizes the VDR protein, thus increasing its half-life (Arbour et al., 1993; Davoodi et al., 1995; Wiese et al., 1992). Recent

work in mouse osteoblastic cells identified functional vitamin D₃ response elements located within intronic regions of the VDR gene, supporting a direct transcriptional mechanism for VDR autoinduction (Zella et al., 2006). Recently, Zella et al. (2010) used chromatin immunoprecipitation scanning to identify two other potential vitamin D₃ response elements, one located 6 kb upstream of the transcription start site of the mouse VDR gene (Zella et al., 2010); however, whether these DNA sequences mediate VDR actions *in vivo* is uncertain.

3. Thyroid Hormone Receptor (TR)—Thyroid hormone receptors exhibit autoinduction and autorepression, although the former has been best documented and studied. The most detailed studies of TR autoregulation have been conducted on tadpoles of the South African clawed frog *Xenopus laevis*. Tadpole metamorphosis is dependent on TH, and TR autoinduction is hypothesized to be essential to the metamorphic process. Similar phenomena may occur in developing mammalian brain, although this has received less attention.

Autoinduction: One of the better understood examples of NR autoinduction and its biological significance is the autoinduction of the beta isoform of the TH receptor (TR) that occurs during amphibian metamorphosis. The transformation of a tadpole into a frog is dependent on TH, and TH biosynthesis and secretion increases during metamorphosis reaching a peak at metamorphic climax (reviewed by Denver, 2009a). The frog *X. laevis*, like all jawed vertebrates studied to date, has two TH receptor subtypes, TR α and TR β encoded by four genes (TR α A and B, TR β A and B) owing to its pseudotetraploidy (Yaoita et al., 1990). The mRNAs for TR subtypes are detected at the time of hatching, and expression of TR α increases shortly thereafter to reach peak levels in the tadpole that are sustained through metamorphosis (Shi, 2000). By contrast, after hatching TR β mRNA expression is very low, but then rises in parallel with the elevation in plasma TH that occurs during metamorphosis, reaching a peak at metamorphic climax that coincides with maximal production of TH and a period of rapid tissue transformation (Shi, 2000). Autoinduction of TR β is also seen in *X. laevis* tissue culture cells (i.e. XTC-2 and XL177), which has allowed for detailed investigations of response kinetics and molecular mechanisms of gene regulation (Kanamori and Brown, 1992; Machuca and Tata, 1992).

The patterns of TR α and TR β expression in rat brain parallel those seen in the tadpole during metamorphosis. For example, TR α expression is high and relatively constant throughout late fetal and neonatal periods; whereas, TR β expression is low at birth and shows a dramatic increase during the first 2 weeks postnatally that is coincident with rising plasma TH concentrations (Strait et al., 1990). The human TR β promoter has two functional TREs that mediate transactivation in transient transfection assays (discussed below), but to our knowledge, the occurrence and significance of TR β autoinduction during mammalian development has not been investigated.

Autorepression: Examples of autorepression of TR genes are isoform specific and have been seen mostly in pituitary cells. Thyroid hormone treatment of a rat pituitary tumor cell line, GH1, decreased TR receptor number as measured by nuclear 3,5,3'-triiodothyronine (T₃) binding capacity (Samuels et al., 1977). In rats, TR β 2 (a TR β isoform generated by alternative splicing) is elevated in the hypothyroid state, which becomes normalized or decreased below basal in the transition to the euthyroid or hypothyroid state, respectively (Childs et al., 1991; Ercan-Fang et al., 1996; Hodin et al., 1990.) However, there were no changes in nuclear TR binding capacity when TR β 2 mRNA was decreased, thus questioning the physiological relevance of the downregulation of the TR β 2 gene (Ercan-Fang et al., 1996; Hodin et al., 1990).

Molecular mechanisms of TR autoregulation: Autoinduction of TR β in the tadpole can be explained by the presence of TH response elements (TREs) located in the proximal promoter region of the genes (Ranjan et al., 1994; Machuca et al., 1995). The proximal TR β A promoter of *X. laevis* contains three putative TREs, two of which are near optimal direct repeat +4 (DR+4) TREs and are located just upstream or proximal to the transcription start site (Machuca et al., 1995; Ranjan et al., 1994). Transfection assays and mutational analysis have shown that both DR+4 TREs support TH-dependent transactivation, and also transrepression in the absence of TH. TR-RXR heterodimers, but not TR or RXR homodimers bound the DR+4 regions in a ligand-dependent manner (Machuca et al., 1995; Ranjan et al., 1994; Ulisse et al., 1996). The human TR β gene has two functional TREs located in the 5' flanking region that mediate autoinduction in transient transfection assays using the rat pituitary tumor cell line GH3 (Sakurai et al., 1992; Suzuki et al., 1994).

Further support for the functionality of the proximal TRE in the *X. laevis* TR β A promoter was shown by studies using a promoter-reporter construct transfected into living tadpole tail muscle *in vivo* (Ulisse et al., 1996). Treatment with TH activated transcription of a TR β A promoter-reporter construct containing the proximal DR+4 TRE cotransfected with TR β expression plasmids. This activity was abolished by cotransfection of a mutant TR β capable of binding DNA but not hormone (Ulisse et al., 1996). Taken together, both *in vitro* and *in vivo* experiments support that the frog TR β A gene is a direct TR target. However, TH induction of TR β was found to be partially sensitive to protein synthesis inhibition (Kanamori and Brown, 1992; Machuca and Tata, 1992), suggesting that the synthesis of proteins other than preexisting TRs may be required for full TR β autoinduction.

Autoinduction of TR β was originally thought to be the earliest TH response in premetamorphic tadpole tissues (Yaoita and Brown, 1990), but it was subsequently discovered, through the use of gene expression screens, that other genes respond to TH more rapidly than TR β (Shi, 2000). One of the most rapidly responding TH-induced genes in tadpole tissues is the transcription factor Krüppel-like factor 9 (KLF9; also known as basic transcription element binding protein 1; BTEB1). In *X. laevis* tadpole tissues (brain, tail, intestine), KLF9 is the most rapidly responding TH-induced gene, and its expression parallels the increase in plasma TH that occurs during tadpole metamorphosis (Denver, 1997; Furlow and Kanamori, 2002; Gomez et al., 1996; Hoopfer et al., 2002; Shi, 2000; Wang and Brown, 1993). The TH responsiveness of the frog gene is attributed to a near perfect DR+4 TRE located ~6.5 kb upstream of the transcription start site (Furlow and Kanamori, 2002); TREs have also been described in mammalian KLF9 genes (Denver and Williamson, 2009); P. Bagamasbad and R.J. Denver, unpublished data).

As mentioned above, although TREs were identified in the frog TR β A gene, studies with the protein synthesis inhibitor cycloheximide suggested that the synthesis of other factors was necessary for maximal TR β autoinduction. The discovery that KLF9 is a rapidly responding TH-induced gene, and that the TR β A promoter has several potential binding sites for KLF9 (Ranjan et al., 1994) led to the hypothesis that TR β A is a target gene for KLF9 (Bagamasbad et al., 2008). Analysis of the kinetics of expression of TR β A and KLF9 mRNAs showed that KLF9 is upregulated earlier than TR β A in cultured *Xenopus* fibroblast cells (XTC-2) and in the brain of premetamorphic tadpoles treated with TH (Bagamasbad et al., 2008). Electrophoretic mobility shift assays showed that KLF9 can bind to GC rich regions of the proximal TR β A promoter, and chromatin-immunoprecipitation (ChIP) assays found KLF9 associates with this region *in vivo* in a TH and developmental stage-dependent manner. Moreover, forced expression of KLF9 in XTC-2 cells or tadpole brain *in vivo* accelerated and enhanced TR β A autoinduction (Bagamasbad et al., 2008; F. Hu, P. Bagamasbad and R.J. Denver, unpublished). These findings support the hypothesis that the

immediate early gene KLF9 functions as an accessory transcription factor necessary for TR β autoinduction.

Physiological significance of TR autoinduction: The discovery that TR β was autoinduced in tadpole tissues led to the hypothesis that the increase in TR β is necessary for driving metamorphosis, whereas, the early expression of TR α was necessary to establish tissue competence to respond to the hormone (Tata, 2000). There are at least two potential mechanisms by which TR β autoinduction could function to promote metamorphosis: 1) Receptor autoinduction could cause a general increase in tissue sensitivity to TH, thereby amplifying gene expression responses to TH, or 2) TR β could regulate a set of genes/ processes that are distinct from those regulated by TR α . There are several lines of evidence that support a role for TR α in establishing tissue competence to respond to TH, and in the proliferative actions of the hormone, which are the earliest responses to TH that occur in target tissues. Studies of the temporal and spatial expression of the different TR subtypes, and the use of TR subtype-specific TH analogs support a role for TR α in cell proliferation in the hindlimb and brain. By contrast to TR α , the expression pattern of TR β is dependent on the rise in plasma TH during metamorphosis, and findings using the TR β specific TH analogs GC1 and GC24 support the hypothesis that TR β functions in cell differentiation and apoptosis (reviewed by Furlow and Neff, 2006; Denver et al., 2009)

Other lines of evidence support a role for TR β autoinduction during metamorphosis. For example, treatment with prolactin, which blocked TH-induced tadpole limb bud growth and tail regression, decreased TR α and completely blocked TR β autoinduction (Baker and Tata, 1992; Tata et al., 1991). These correlative data suggest that one mechanism by which prolactin blocks metamorphosis is through inhibition of TR β autoinduction, and therefore that TR β autoinduction is necessary for tissue transformations.

Obligate paedomorphic salamanders (they attain reproductive maturity while retaining larval characteristics) do not respond to TH by initiating metamorphosis. Safi et al. (1997) failed to find evidence for expression of TR β mRNA in the mudpuppy *Necturus maculosus* using reverse transcriptase polymerase chain reaction, and suggested that this may be the reason that the animals do not respond to TH by metamorphosing. However, this species was found to have genes for both TR subtypes that are expressed in some tissues and code for functional proteins as evidenced by DNA binding, hormone binding, and transactivation of target genes in *in vitro* transfection assays (Safi et al., 2006). Contrary to the initial report, Safi et al. (2006) have since found that both TRs are expressed in different tissues at low levels in *N. maculosus*, but TR β shows no, or only modest responses to high doses of TH in gill and tail fin, two structures that undergo apoptosis in metamorphosing salamanders but not in *N. maculosus* (Safi et al., 2006). However, TR β may be induced in the brain of the mudpuppy where TH responses may have been retained to support neurological development (M. Miller and R.J. Denver, unpublished). Safi and colleagues suggested that loss of metamorphosis in the lineage of salamanders that includes *N. maculosus* may have depended on the loss of TH-dependent control of key genes required for tissue transformation. However, it is also possible that the failure to upregulate TR β in organs that normally undergo metamorphic transformation in metamorphosing species (e.g., the gill, tail, etc.) is responsible for the paedomorphic life history.

III. Nuclear Receptor Cross-regulation

In addition to hormones autoregulating expression of their receptor, the regulation of expression of other NRs (cross-regulation) is an important means for modulating cellular responsiveness to different hormonal signals. Nuclear receptor cross-regulation is complex and can take different forms; e.g., the regulation can be unidirectional positive or negative

(Fig. 2A), reciprocal positive (Fig. 2B), reciprocal negative (Fig. 2C), or reciprocal positive and negative; Fig. 2D). Also, cross-regulation can operate at both transcriptional and posttranscriptional levels (see Fig. 1).

Nuclear receptor cross-regulation is a means to coordinate, in a temporal manner, the responsiveness of a cell to a subsequent (different) hormonal signal, or to allow for crosstalk between hormonal signaling pathways. For example, cross-regulation between ER and PR is important for the morphological changes in the uterus, and the expression of female sexual behavior that occurs during the mammalian ovarian cycle. During amphibian metamorphosis cross-regulation between GR and TRs sensitizes tissues to the TH signal, thereby accelerating metamorphosis. These and other examples of NR cross-regulation are discussed below. This survey is not comprehensive, and new examples of NR cross-regulation continue to be discovered. Our goal is to provide a few examples of NR cross-regulation covering the different forms that it can take that are described above and depicted in Fig. 2.

A. Cross-regulation Between Estrogen and Progesterin Receptors

One of the better studied forms of NR cross-regulation is the reciprocal positive and negative regulation between the ER and PR that occurs during mammalian ovarian cycles; liganded ER upregulates PR, but liganded PR downregulates ER expression. During the rodent estrous cycle circulating estrogen concentrations rise at the beginning of proestrus and reach peak levels during mid-proestrus prior to the LH surge (reviewed by McCarthy and Becker, 2002). Progesterone increases at late proestrus and peaks during the transition from proestrus to estrus. These cyclical hormonal changes cause increased cell proliferation and differentiation of uterine cells and initiate female sexual behavior.

Rising plasma estrogen concentration promotes proliferation of uterine epithelial cells (the proliferative phase; Quarmby and Korach, 1984). After ovulation, the uterine epithelium shifts from proliferation to secretion, mediated by the actions of progesterone. Progesterone blocks estrogen-dependent epithelial cell proliferation, promotes proliferation and differentiation of uterine stromal cells (decidualization) and if pregnancy occurs, it suppresses myometrial contractions (reviewed by Graham and Clarke, 1997). These opposing and compartment-specific effects of estrogen and progesterone can be explained by cross-regulation of their NRs.

Estrogen acts on the uterus causing ER autoinduction (discussed earlier) and increased PR mRNA and protein (Evans and Leavitt, 1980; Kamiya et al., 1996; Kraus and Katzenellenbogen, 1993; Tibbetts et al., 1998; Yamashita et al., 1990). The molecular basis for the estrogen-dependent upregulation of PR is attributed to functional estrogen responsive elements (ERE) in the promoter region of the PR gene (Kraus et al., 1993; Kraus et al., 1994). Support for positive cross-regulation of PR by ER *in vivo* comes from studies of ER α knockout mice where PR was expressed in the uterus, but could not be induced by estrogen (Couse et al., 1995).

The upregulation of PR by liganded ER is important for sensitizing uterine cells to the actions of progesterone, the plasma concentration of which peaks shortly after the estrogen surge during the ovarian cycle. On the other hand, progesterone blocks the estrogen-mediated increase in ER and PR (Evans and Leavitt, 1980; Kraus and Katzenellenbogen, 1993), and the progesterone-mediated block of ER autoinduction is accompanied by inhibition of epithelial cell proliferation at the beginning of the secretory phase. The elevated plasma concentration of estrogen increased PR expression, and uterine stromal cells are thus sensitized to the rising plasma concentration of progesterone that promotes decidualization. Thus, cross-regulation of ER and PR expression is central to the

morphological and physiological changes that occur in uterine cells during the mammalian ovarian cycle (Graham and Clarke, 1997).

Estrogen and progesterone produced during the ovarian cycle act on the brain to promote female sexual behavior (lordosis; McCarthy and Becker, 2002). Progesterone acting through the PR is necessary for the expression of lordosis. Exposure to estrogen (priming) appears necessary for the subsequent action of progesterone to 'release' the behavior. Studies in rats and guinea pigs showed that estrogen induces PR expression in the hypothalamus and preoptic area (reviewed by McCarthy and Becker, 2002). In ovariectomized guinea pigs, only animals primed with estrogen responded to a subsequent injection of progesterone by exhibiting lordosis behavior, supporting an important role for the estrogen-dependent increase in PR for inducing sexual receptivity during the estrous cycle (Blaustein and Feder, 1979; Blaustein and Turcotte, 1989; DonCarlos et al., 1989; Parsons et al., 1981).

B. Cross-regulation Between Sex Steroid and Glucocorticoid Receptors

Reciprocal regulation occurs between hormones of the reproductive and stress axes. For example, glucocorticoids act at several levels of the hypothalamo-pituitary-gonadal (HPG) axis to inhibit sex steroid biosynthesis and secretion. Sex steroids are also known to influence HPA axis function, and there are sex differences in the regulation of the HPA axis; e.g., testosterone inhibits, while estrogen enhances HPA activity (Handa et al., 1994; McEwen, 1994; Viau, 2002). However, despite the large amount of information on the interaction between the stress and gonad axes, few studies have investigated cross-regulation among NRs that mediate the actions of sex steroids and corticosteroids.

Evidence for cross-regulation between sex steroid receptors (AR and ER) and the GR shows that the regulation is mostly unidirectional and negative, with the sex steroids downregulating GR expression. For example, injections of testosterone or estrogen in rats decreased GR mRNA levels in the hippocampus (Burgess and Handa, 1993; Kerr et al., 1996). A similar phenomenon was observed in the rat lung where antenatal testosterone treatment decreased GR mRNA and protein levels, consistent with the inhibitory effect of androgens on fetal lung development (fetal lung development is dependent on glucocorticoids; Swezey et al., 1998).

Glucocorticoids and estrogens have been shown to have opposing actions in some tissues commonly targeted by both hormones. Estrogen, together with progesterone, is critical for normal mammary gland development where it promotes cell proliferation (reviewed by Sutherland et al., 1998). In breast cancer cell lines, glucocorticoids prevent estrogen-mediated cell proliferation and the increase in PR expression (Zhou et al., 1989). Antagonistic actions between glucocorticoids and estrogen are also observed in bone, where estrogens reduce bone loss while glucocorticoids promote it (Gallagher et al., 2001; Rackoff and Rosen, 1998). The opposing effects of these two hormones may be explained by the cross-regulation of their NRs. For example, in a breast cancer cell line, estrogen repressed GR-mediated transcription from the synthetic MMTV promoter that contains a glucocorticoid response element, and from GR target genes. This repression was due, at least in part, to estrogen inducing the expression of Mdm2, an E3 ubiquitin ligase, that targets GR for proteasomal degradation (Kinyamu and Archer, 2003).

By contrast to the negative cross-regulation between ER and GR in mammary cells, glucocorticoids potentiated ER autoinduction, and the expression of the ER target gene vitellogenin in cultured *X. laevis* hepatocytes (Ulissee and Tata, 1994) suggesting that the interplay between the ER and GR may be tissue specific (or perhaps species specific). More study is needed to understand interactions between the stress and reproductive axes

occurring through cross-regulation among the NRs that mediate sex steroid and corticosteroid actions.

C. Cross-regulation Between Estrogen and Thyroid Hormone Receptors

Thyroid hormone regulates diverse developmental and physiological processes such as brain development, growth, energy metabolism and reproduction. Estrogen plays a critical role in reproductive development, physiology and sexual behavior. These two endocrine systems interact to influence aspects of reproduction and sexual behavior. For example, TH and estrogen cooperate to regulate the synthesis of yolk proteins by the liver in frogs. Thyroid hormone potentiated ER autoinduction in primary cultures of frog (*X. laevis*) hepatocytes, and in the liver *in vivo* (Rabelo and Tata, 1993; Ulisse and Tata, 1994). Thyroid hormone treatment also accelerated the upregulation of the estrogen target gene vitellogenin. This ability of TH to enhance ER autoinduction in the liver is developmental stage-dependent, appearing at metamorphic climax (May and Knowland, 1980; Rabelo et al., 1994). Thyroid hormone induction of ER gene expression has also been reported in rat liver, although whether it potentiates ER autoinduction was not investigated (Freyschuss et al., 1994).

Cross-regulation between TH and ER has also been observed in the tadpole brain (*Rana pipiens*) (Hogan et al., 2007), and TH increased ER α mRNA in GH3 cells, thereby potentiating the actions of estrogen (Fujimoto et al., 2004; Fujimoto et al., 1997). To our knowledge, TREs have not yet been demonstrated in ER genes of any species, and the molecular basis for the cross-regulation of ER expression by TR is not understood.

Thyroid hormone and estrogen play central roles in the control of sexual behavior. Interplay between TH and estrogen actions on the brain may provide a mechanism for assessing metabolic state, thus affecting reproductive physiology and behavior. For example, in birds and mammals TH promotes the transition to anestrus. In some mammals, exposure to cold temperatures increases plasma TH levels, suggesting that the cross-regulation between TH and estrogen is involved in mediating environmental effects on reproductive behavior (reviewed by Vasudevan et al., 2002). In rodents, TH decreases estrogen-dependent lordosis behavior. For example, in ovariectomized (OVX) rats and mice, estrogen replacement plus TH treatment decreased lordosis behavior compared to estrogen replacement alone (Dellovade et al., 1996; Morgan et al., 2000). Similarly, thyroid-intact, OVX female rats that received estrogen replacement showed delayed onset of lordosis behavior compared to animals that were thyroidectomized, OVX+estrogen (Dellovade et al., 1996). In addition, TR β knockout mice that were OVX+estrogen showed increased lordosis behavior as compared to wild type OVX+estrogen mice; whereas, the same experimental paradigm comparing TR α knockout mice showed decreased sexual receptivity compared to wild type (Dellovade et al., 2000), suggesting that the actions of TH on sexual behavior are complex and TR subtype-specific.

The findings described above suggested the hypothesis that TH inhibits lordosis behavior by decreasing plasma estrogen levels, or by decreasing ER expression in the hypothalamus. However, TH administration did not affect plasma estrogen levels (Dellovade et al., 1996; Morgan et al., 2000), and instead increased ER immunoreactivity in the hypothalamus (Dellovade et al., 1996), which suggested that TH effects on lordosis may not be mediated through effects on ER signaling. Subsequent studies investigated possible effects of TH on the expression of estrogen target genes in the brain that are known to be involved in sexual behavior (Dellovade et al., 2000; Scott et al., 1997; Vasudevan et al., 2001a; Vasudevan et al., 2001c; Zhu et al., 2001; Zhu et al., 1996). For example, expression of the oxytocin gene, which is a known ER target, was downregulated by TH, and this action was TR subtype-specific (Dellovade et al., 2000; Vasudevan et al., 2001b). Estrogen-dependent induction of the preproenkephalin (PPE) gene was also attenuated by TH (Vasudevan et al., 2001c; Zhu

et al., 2001; Zhu et al., 1996). Molecular analysis of the cross-regulation between TH and estrogen in the regulation of the PPE gene found that TR and ER both associate with the same segment of DNA located in the PPE promoter (a predicted ERE; Vasudevan et al., 2001c; Zhu et al., 2001). Since both ER and TR have identical consensus hormone response element half sites (Glass et al., 1988; Truss and Beato, 1993) and TR can bind to the EREs of ER target genes, TR may decrease lordosis behavior by inhibiting ER transactivation through competition with ER for DNA binding, or perhaps through protein-protein interactions (Vasudevan et al., 2001a; Zhu et al., 2001). Another proposed mechanism is competition between TR and ER for coactivators such as SRC-1 (Vasudevan et al., 2001a; Vasudevan et al., 2001b).

D. Crossregulation Between Thyroid Hormone and Glucocorticoid Receptors

The thyroid and stress endocrine axes interact at multiple levels to influence development, physiology and behavior. Here we focus on the cross-regulation of NRs for TH and corticosteroids. In amphibians and other nonmammalian species, interactions between the thyroid and stress endocrine axes have been demonstrated at both central and peripheral levels. Hypothalamic CRF regulates both the stress and thyroid axes by stimulating secretion of ACTH and TSH (De Groef et al., 2006). In amphibians, this dual role for CRF allows tadpoles to modify their rate of metamorphosis in response to a changing environment (Denver, 1997; Denver, 2009b). At the periphery, corticosteroids synergize with TH to accelerate metamorphosis, and it is at this level that NR cross-regulation has been observed (Denver, 2009b).

In tadpole tail, corticosteroid treatment accelerated TH-induced tail shrinkage, a measure of metamorphic progression (reviewed by Denver, 2009b). Treatment of tadpole tail explants with corticosteroids increased nuclear binding capacity for TH (Kikuyama et al., 1983; Suzuki and Kikuyama, 1983) and TR mRNAs; similar findings on corticosteroid actions on TR mRNA expression were observed in tadpole tail, intestine and brain *in vivo* (Krain and Denver, 2004; R. Bonett, E.D. Hoopfer and R.J. Denver, unpublished data). These findings suggest that corticosteroids can enhance sensitivity of target tissues to TH by increasing the expression of TRs, thus accelerating metamorphosis. Corticosteroids have also been shown to increase expression of type 2 deiodinase in tadpole tissues, which catalyzes the conversion of thyroxine (T₄) to the more active form T₃ (Galton, 1990; R. Bonett, E.D. Hoopfer and R.J. Denver, unpublished data). This would increase bioavailability of the ligand for TR, and thus facilitate TH action on target tissues.

There is also evidence that TH can regulate GR mRNA in some tadpole tissues. Treatment of tadpoles with T₃ downregulated GR mRNA in brain and intestine, but upregulated it in tail (Krain and Denver, 2004). The synergistic actions of TH and corticosteroids on tadpole tail shrinkage may be explained, in part, by the reciprocal positive cross-regulation of TR and GR, which would sensitize the tissue to further hormone action.

The molecular basis for GR (or MR) regulation of TR gene expression has not been investigated. Therefore, it is not known whether this regulation is direct on TR gene transcription, or indirect through induction of other transcription factors, or through effects on mRNA transcript or protein stabilization. We recently found that KLF9, which we earlier showed could associate with the frog TR β A promoter and enhance autoinduction, is a direct GR target gene in frog and mouse brain (Bonett et al., 2009; P. Bagamasbad, T. Ziera, S.A. Borden and R.J. Denver, unpublished data). Thus, one mechanism by which corticosteroids may increase TR β gene expression is through induction of KLF9 (see Fig. 3). In this regard, it is noteworthy that combined treatment with TH and corticosterone synergistically activated KLF9 transcription in frog and mouse brain (R. Bonett, P. Bagamasbad and R.J. Denver, unpublished).

Conclusions

Nuclear receptor auto- and cross-regulation are important mechanisms for amplifying hormone signals, regulating hormone activity through negative feedback, and coordinating hormone action in a temporal and tissue-specific manner. In this review we have highlighted some of the better known examples of auto- and cross-regulation of classical nuclear hormone receptors, but there are other examples not discussed here, and perhaps many more to be discovered. Also, other classes of NR genes may be similarly auto- or cross-regulated.

Autoinduction of NR genes appears to have arisen very early in animal evolution and may have been maintained by natural selection because of a pivotal role in controlling development. This feed-forward mechanism may be essential for developmental progression from larva or fetus to the juvenile adult animal. While this conclusion is supported by correlational data and some functional studies, direct tests are still needed to understand the importance of NR autoinduction to animal development and physiology.

Auto- and cross-regulation can occur through mechanisms that involve direct DNA binding of NRs to the homologous NR gene, or through indirect transcriptional or posttranscriptional mechanisms. While some of these mechanisms have been elucidated for some NRs, much remains to be learned about the physiological and molecular mechanisms that regulate NR gene expression. Elucidating these mechanisms is essential to understand the diverse roles that NRs play in animal development, and in adult physiology and behavior.

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Figure 1.

Molecular mechanisms for regulation of nuclear receptor (NR) expression. The level of functional NRs in a cell can be regulated at transcriptional or posttranscriptional levels, or some combination of the two. **A.** Direct transcriptional regulation involves the hormone (filled oval)-NR complex (NRA; shown as a homodimer, but type II NRs also function as heterodimers) directly binding to a hormone response element located within the *nra* gene that activates or represses its expression (for cross-regulation the NRA binds to and regulates a different NR gene). Some NRs may influence target genes through hormone response elements that are far upstream or downstream of the regulated locus. Also, some NRs regulate target genes through protein-protein interactions rather than by direct DNA binding. **B.** Indirect transcriptional regulation involves the hormone-NRA complex inducing the expression of a gene that codes for a transcription factor (TF) that then positively or negatively regulates *nra* gene transcription (for cross-regulation the NRA regulates a TF that binds to and regulate a different NR gene). **C.** Cooperative transcriptional regulation involves both direct and indirect transcriptional mechanisms shown in parts A and B. **D.** The NRA may regulate the expression of a gene that increases or decreases stability of the *nra* mRNA (for cross-regulation, the mRNA for a different NR gene). **E.** Hormone binding to the NRA can stabilize it, thus increasing its half-life ($t_{1/2}$). **F.** The NRA may induce expression of a ubiquitin ligase that ubiquitinates (Ub) NRs in the cell (either the NRA or a different NR) and targets it to the proteasome for degradation. NR protein stability and bioactivity may also be influenced through posttranslational modifications such as (e.g., phosphorylation).

Figure 2.

Forms of nuclear receptor (NR) cross-regulation. Hormone-bound NRs can regulate the expression of other types of NRs, and NR cross-regulation can take several forms. **A.** Unidirectional cross regulation involves a NR (NRA) regulating the expression of a different NR (NRB) while NRB does not affect the expression of NRA. **B.** In reciprocal positive cross-regulation, the hormone-bound NR (NRA) positively regulates the expression of another type of NR (NRB) and at the same time, hormone-bound NRB upregulates the expression of NRA. **C.** Reciprocal negative cross-regulation occurs when a hormone-bound NR (NRA) downregulates expression of another NR (NRB), and hormone-bound NRB negatively regulates expression of NRA. **D.** In another form of cross-regulation, a hormone-bound NR (NRA) positive regulates the expression of another NR (NRB), while NRB downregulates expression of NRA.

Figure 3.

Role of the thyroid hormone (TH)-induced immediate early transcription factor Krüppel-like factor 9 (KLF9) in TH receptor (TR) autoinduction. Ligand-bound TR-retinoid X receptor (RXR) heterodimers bind to and induce expression of *klf9* and *trb* genes. The upregulation of KLF9 by TH precedes TR β . KLF9 associates with the promoter region of TR β and enhances TR β autoinduction (Bagamasbad et al., 2008). Aside from being a TH direct target gene, *klf9* is also a direct glucocorticoid receptor (GR) target gene that is induced by stress (Bonett et al., 2009; P. Bagamasbad, T. Ziera, S.A. Borden and R.J. Denver, unpublished data). Thyroid hormone and glucocorticoids synergistically activate KLF9 expression, thereby further enhancing TR β autoinduction.