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Comparative Neuroendocrinology of Steroid Receptor Gene Expression and Regulation: Relationship to Physiology and Behavior

Larry James Young and David Crews

Great diversity exists among vertebrates in reproductive behaviors and the neuroendocrine mechanisms underlying these behaviors. Comparisons of species with different hormone–brain-behavior relationships reveal three factors which may explain species differences in endocrine physiology and behavior: (a) sensitivity to sex steroid hormones, (b) hormone-dependent regulation of sex steroid hormone receptor gene expression, and (c) neuroanatomical distribution of steroid receptor gene expression, especially in nonlimbic structures. (Trends Endocrinol Metab 1995;6:317–323).

Steroid hormones secreted by the gonads have a profound effect on the reproductive behavior and physiology of vertebrates. Estrogen and progesterone (P) regulate the receptive behavior of females so that mating occurs at the appropriate stage of ovarian activity in many species, whereas testicular androgens activate the courtship and copulatory behavior of males in all vertebrate classes (Crews and Silver 1985, Pfaff and Schwartz-Giblin 1994, Sachs and Meisel 1994). The actions of sex steroid hormones are mediated primarily by ligand-dependent transcription factors that bind to specific sequences of the DNA and alter the transcription rates of downstream genes (Truss and Beato 1993). These receptors are members of an ancient superfamily of genes sharing a similar structure that evolved from a common ancestral gene prior to the divergence of the vertebrate taxa (Laudet et al. 1992). Like the sequence homology of the receptor genes, it is evident that the distribution of sex steroid receptors within the brain has remained remarkably conserved across diverse taxa, particularly within the limbic system (Laudet et al. 1992, Pfaff and Schwartz-Giblin 1994, Sachs and Meisel 1994, Young et al. 1994). Although the distribution of sex steroid receptor-containing neurons are similar across species, each receptor type has its own unique, yet phylogenetically conserved, distribution within the brain.

Great diversity exists in the nature and pattern of reproductive behavior and underlying endocrine physiology in vertebrates, even among mammals (Conaway 1971, Crews 1984). Given this diversity, one can ask if the relationship among sex steroid hormone secretion, sex steroid receptor gene expression in the brain, and the expression of reproductive behavior is as strongly conserved as the phylogenetically stable core distribution of sex steroid hormone-concentrating neurons. Unlike the conserved nature of the limbic distribution of sex steroid receptors, the regulation of sex steroid receptor gene expression appears to be less constrained, and may vary depending upon the reproductive biology of the species. Furthermore, species differences in the abundance of sex steroid receptors in specific brain regions appear to have profound effects on the normal circulating concentrations of sex steroid hormones and the sensitivity to sex steroid hormones. Here, we review species differences in sex steroid receptor expression in the vertebrate brain and discuss their relationship to species differences in endocrine physiology and behavior. Comparison of species with different relationships between sex steroid hormone secretion and the hormonal control of sexual behavior demonstrates the plasticity of the regulation of sex steroid receptor gene expression. Finally, diversity in the distribution of sex steroid receptor reveals the evolutionary significance of changes in their distribution in the vertebrate brain. This information is placed in context by first considering recent research from this laboratory on the evolution and adaptation of neuroendocrine mechanisms controlling sexual behavior.

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• A Model System for the Evolution of Hormone–Brain-Behavior Relationships

The ancestors of most animals are extinct, and postulates of the evolution of brain mechanisms regulating behavior are often speculative at best. If it were possible to compare the neuroendocrine mechanisms that control the sexual behaviors of extant species with those of their ancestral species, however, then this question of the evolution of the neuroendocrine mechanisms controlling behavior might be accessible to researchers.

For the past 17 years, this laboratory has been working with an animal model system, the whiptail lizards (genus *Cnemidophorus*), because they afford a particularly good opportunity to investigate the evolution of the neuroendocrine mechanisms underlying reproduction (Crews 1989). This is because a direct ancestor–descendant phylogeny is present and two different forms of reproduction exist, sexual and asexual. Approximately one-third of extant whiptail lizard species are all-female (parthenogenetic) species resulted from hybrid unions of sexual species (Cole 1975). For example, the parthenogenetic desert-grasslands whiptail (*Cnemidophorus uniparens*) descended from a hybridization event between two sexually reproducing species, the rusty rumped whiptail (*C. burti*) and the little striped whiptail (*C. inornatus*); two-thirds of the triploid genome of the descendant parthenogenetic species is derived from the little striped whiptail, the maternal ancestral species (Densmore et al. 1989).

Although genetically very similar, the desert-grasslands whiptail (hereinafter, the parthenogenetic whiptail) and the little striped whiptail (hereinafter, the sexual whiptail) differ in several aspects of their reproductive biology: (a) estradiol (E2) concentrations in reproductively active parthenogenetic whiptails are approximately five-fold lower than in reproductively active female sexual whiptails (Moore et al. 1985, Moore and Crews 1986), and (b) although the sexual ancestral species display the typical vertebrate pattern, in that the male mounts and intromits and the female is receptive to the male's courtship and copulation, individual parthenogenetic whiptails alternate between displaying male-like pseudocopulatory behaviors and female-like receptive behaviors depending upon the stage of gonadal development (Figure 1) (Crews et al. 1986).

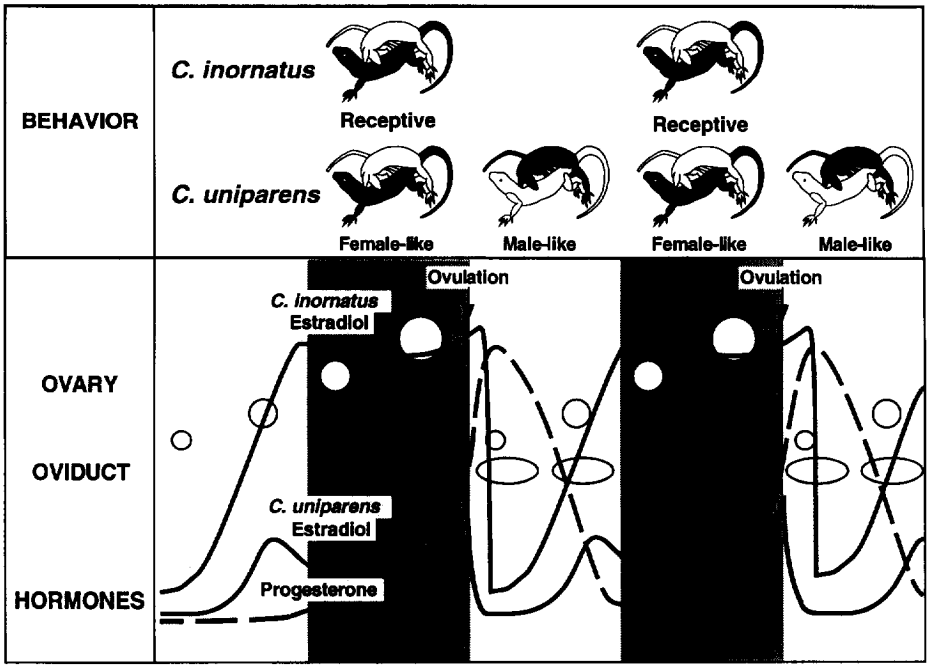

Figure 1. Schematic illustration of the relationship among ovarian development, circulating concentrations of sex steroid hormones, and reproductive behavior in the sexual little striped whiptail (*Cnemidophorus inornatus*) and the unisexual desert-grasslands whiptail (*C. uniparens*). Notice (a) the species differences in circulating concentrations of estradiol and (b) that unlike female whiptails, which typically exhibit sexual receptivity only during vitellogenesis and aggressively reject male courtship advances during the postovulatory period, the parthenogenetic whiptail alternates between expressing female-like receptive behavior and male-like mounting and copulatory behavior, depending upon the gonadal and hormonal condition.

Because changes in the circulating concentrations of sex steroid hormones can have dramatic effects on endocrine physiology and behavior, one might expect the severalfold difference in the circulating concentration of E2 between the parthenogenetic whiptail and the sexual whiptail to be accompanied by species differences in estrogen-dependent phenomena. Whiptail lizards, therefore, provide an opportunity to investigate both the neuroendocrine basis as well as the consequences of species differences in hormone secretion.

The secretion of ovarian sex steroid hormones in vertebrates is under the control of the hypothalamic–pituitary–gonadal axis. Briefly, gonadotropin-releasing hormone (GnRH) released into the portal blood system modulates pituitary gonadotropin secretion. These gonadotropins in turn stimulate an increase in ovarian steroid secretion. Neurons sensitive to circulating concentrations of sex steroid hormones located in the preoptic area (POA) monitor the concentration of E2 in the circulation. In many species, GnRH release is inhibited when concentrations of E2 are elevated above some threshold level, indicating that E2 secretion is under negative feedback control.

Comparisons of ER-mRNA content in the brain of whiptail lizards indicate that parthenogenetic whiptails have higher concentrations of ER-mRNA expression in the POA than do female whiptails (Figure 2) (Young et al. 1995b). Thus, an inverse relationship exists between sex steroid receptor gene expression in the POA and circulating sex steroid hormone concentration. The increased level of ER gene expression in the POA may result in a greater sensitivity to the circulating concentrations of E2, which could in turn result in lower levels of circulating E2 through feedback effects. This sensitivity compensation model is illustrated in Figure 3.

Why is ER-mRNA expression in the POA higher in the parthenogenetic whiptail than in its maternal ancestral species? One possibility is that it is linked to the increased gene dosage resulting from the triploid nature of the genome. It has been suggested that one reason that polyploid species differ physiologically and ecologically from their diploid relatives is that the in-

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creased gene dosage may result in higher enzyme and hormone levels (Futuyma 1986). This phenomenon has been well documented for a number of enzymes in several plant species (Levin 1983). Allozyme analysis of a number of diploid and polyploid whiptail lizards, including the parthenogenetic whiptail, demonstrate that each of the three sets of chromosomes is actively transcribing genes at rates proportional to the gene dosage (Neaves and Gerald 1968, Dessauer and Cole 1984), rather than one chromosome set becoming inactivated as might be expected. Triploidy, therefore, could result in increased sensitivity to estrogen not only by increasing the basal rate of ER production, but also by increasing estrogen-dependent target gene transcription rates, as the target gene number is also increased.

The species differences in circulating concentrations in E2 and estrogen receptor mRNA are accompanied by differences in sensitivity to E2. Dose-response studies reveal that lower dosages of estradiol benzoate (EB) are required to induce receptive behavior, as well as changes in gene expression in the ventromedial nucleus of the hypothalamus (VMH) of parthenogenetic whiptails compared with sexual whiptails (Fig. 4) (Young et al. 1995d). As in other vertebrates, the VMH is involved in the hormonal induction of receptive behavior in whiptail lizards (Wade and Crews 1991, Kendrick et al. 1995).

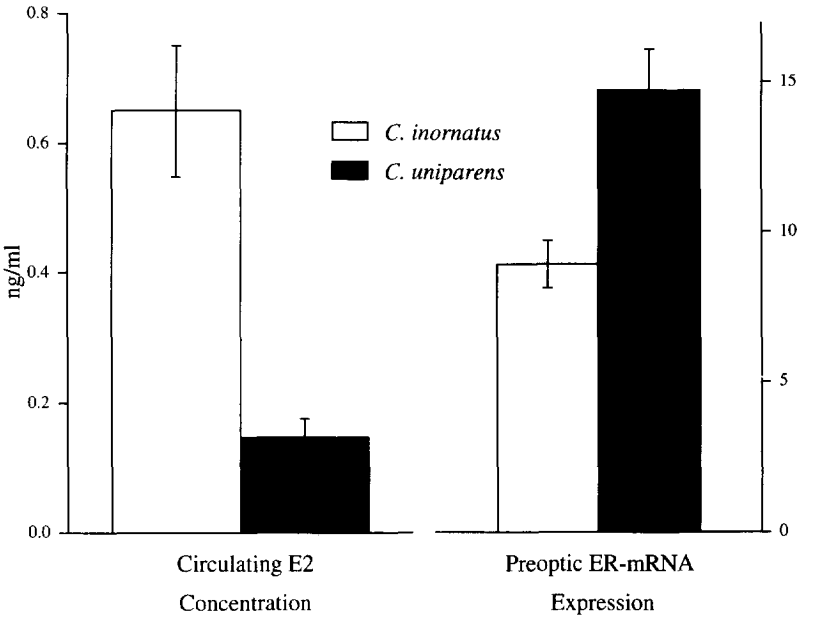


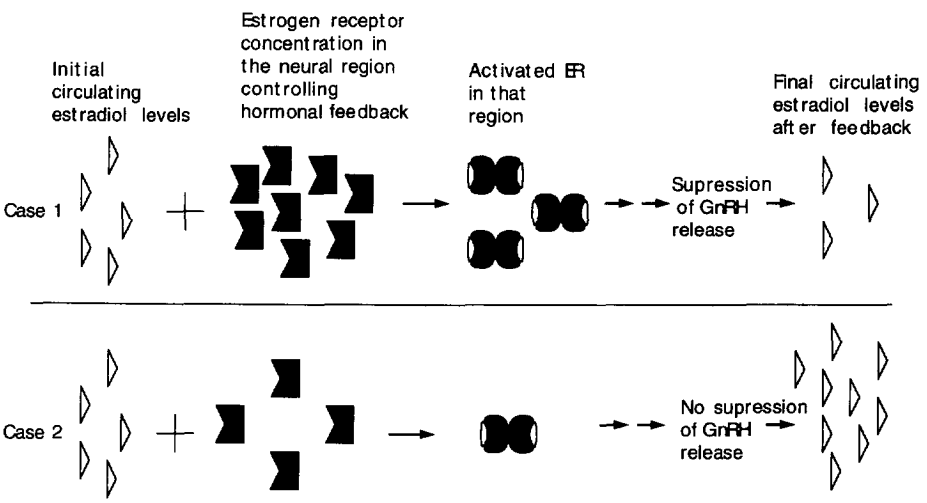
Figure 2. Circulating estradiol concentrations and estrogen receptor (ER)-mRNA expression in the preoptic area of the vitellogenic female whiptail (*Cnemidophorus inornatus*) and the parthenogenetic whiptail (*C. uniparens*). Estradiol concentrations were determined by RIA (Moore et al. 1985 Moore and Crews 1986) and ER-mRNA expression was determined by in situ hybridization (Young et al. 1995b). *Vertical error bars* represent standard errors of the mean.

• Comparisons Among Other Vertebrates Species Differences in Sensitivity to Sex Steroid Hormone

Species differences in sex steroid receptor abundance and sensitivity to sex steroid hormones may be fairly common. Something similar to our sensitivity compensation model has been reported among old world and new world monkeys (Lipsett et al. 1985). Typical plasma sex steroid hormone levels are elevated twofold to fivefold for E2 and up to 100-fold for P in new world monkeys compared with old world monkeys. Although brain tissues were not analyzed in these studies, sex steroid receptor binding assays of peripheral tissues reveal a greater abundance of ER and PR in old world monkeys than in new world monkeys. Again, there is an inverse relationship between sex steroid receptor abundance and circulating hormone concentrations.

Comparison of rodent species reveals another example of sensitivity compensation. Circulating concentrations of E2 during proestrus in laboratory rats, guinea pigs, and hamsters are 50, 70, and 190 pg/mL, respectively (Feder 1985). These species also differ in their sensitivity to exogenous estrogen. The induction of lordosis in ovariectomized females by estrogen treatment requires 1–2 mg/kg body weight in laboratory rats (Powers and Valenstein 1972), 2–5 mg/kg body weight in guinea pigs, and 90 mg/kg body weight in hamsters (Fed-

Figure 3. Schematic illustrating the "sensitivity compensation" model for species differences in the circulating concentrations of sex steroid hormones. Two different situations (that is, two different species) are illustrated that differ in the abundance of estrogen receptors (ER) in the neurons involved in the negative feedback loop. Under the initial conditions illustrated, both systems are presented with identical hormone concentrations. However, due to differences in the number of receptor molecules, the neurons in Case 1 have more activated estrogen receptor, which results in an inhibition of GnRH release and, ultimately, a lower circulating concentration of hormone. In Case 2, fewer activated receptors are formed, GnRH release is not inhibited significantly, and hormone levels remain the same or rise.



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er et al. 1974). These differences in sensitivity to estrogen are paralleled by differences in estrogen binding capacity in the brain. In a comparative study of neural uptake of tritiated E2 in the hypothalamus, the laboratory rat and guinea pig bound 3–5 times the amount of E2 as the hamster (Feder et al. 1974). Again, sensitivity to sex steroid hormone is proportional to brain sex steroid receptor abundance and inversely proportional to the normal circulating concentrations of sex steroid hormone.

Another noteworthy example of taxonomic differences in sex steroid receptor abundance is the goldfish. Goldfish have up to 100-fold greater abundance of androgen receptor (AR) in the brain compared with that in the laboratory rat (Pasmanik and Callard 1988). The elevated levels of AR in the goldfish brain may be compensating for the unusually high levels of aromatase activity in the brain, which would tend to deplete the tissue of androgens.

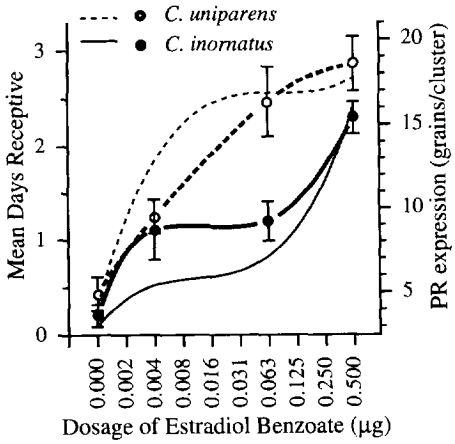

Figure 4. Species (*Cnemidophorus uniparens and C. inornatus*) differences in the induction of sexual receptivity (*thin lines*) and progesterone receptor mRNA expression (*thick lines*) by estradiol benzoate (EB) in ovariectomized whiptail lizards. Ovariectomized animals were given a single injection of EB and either tested daily for receptivity for four days following the injection or brains were removed 24 hours after treatment and analyzed using in situ hybridization. *Vertical error bars* represent standard errors of the mean.

• Hormonal Regulation of Sex Steroid Receptor mRNA Expression

A characteristic of the vertebrate ovarian cycle is that the growing follicle(s) secretes increasing amounts of E2, which begin to decline around the time of ovulation. At the same time circulating concentrations of P increase and peak after formation of the corpus luteum (Feder 1985). In the brain, sex steroid receptor gene expression also changes with follicular development as a function of circulating sex steroid hormone concentrations (Lauber et al. 1990 and 1991a, Simerly and Young 1991, Shughrue et al. 1992, Lisciotto and Morrell 1993, Young et al. 1995b). The hormonal regulation of sex steroid receptor gene expression in the brain is region specific. For example, in the female laboratory rat, treatment with exogenous EB increases PR-mRNA expression in the VMH and the arcuate nucleus, but not in the amygdala (Lauber et al. 1991b). In the whiptail lizard, EB increases ER-mRNA expression in the VMH, decreases ER-mRNA expression in the lateral septum, and has no effect on ER-mRNA expression in the dorsal hypothalamus (Young et al. 1995c). The region-specific regulation of ER protein is further complicated, as ER-mRNA content does not always translate into functional ER protein concentrations, indicating region-specific posttranscriptional processing (Rosenblatt et al. 1994).

One might expect that the hormonal regulation of sex steroid receptor gene expression and, hence, sensitivity to sex steroid hormone, should correspond to the reproductive physiology of the species. The control of PR–mRNA in the hypothalamus provides an example of this phenomenon. Estrogen increases PR concentration in the hypothalamus of many vertebrate species. In some species, including commonly used laboratory rodents (Pfaff and Schwartz-Giblin 1994) and the green anole lizard (Wu et al. 1985), the periovulatory surge in P is involved in the initiation of receptive behavior in females. In these species, a peak in E2 concentration precedes the elevation of P in the ovarian cycle, sensitizing the VMH to the forthcoming P. In the cat, however, P does not play a significant role in the induction of receptive behavior (Michael and Scott 1964) and estrogen treatment has little or no effect on PR immunoreactivity in the VMH (Bayliss et al. 1991).

The regulation of brain ER-mRNA by estrogen has been well characterized only in the laboratory rat and, more recently, in whiptail lizards. A comparison of the estrogenic regulation of ER-mRNA expression between the laboratory rat and whiptail lizards indicates that the regulation of ER-mRNA differs between species as a function of reproductive physiology. Estrogen treatment decreases ER-mRNA expression in the VMH in the female laboratory rat (Lauber et al. 1990, Simerly and Young 1991), yet increases ER-mRNA expression in the VMH of the female whiptail lizard (Young et al. 1995c and d, Godwin and Crews 1995). This species difference is paralleled in the reproductive tract; estrogen treatment decreases ER-mRNA expression in the uterus (Shupnik et al. 1989), while increasing ER-mRNA expression in the whiptail oviduct (Young et al. 1995a). These species differences may be due to the differences in reproductive physiology between laboratory rats and whiptail lizards, a difference that may extend to other vertebrates with extended follicular phases (Figure 5).

The female laboratory rat is unusual in that it has a 4-day ovarian cycle, during which behavioral estrus occurs on the night following the E2 surge of proestrus. In other amniote vertebrates, such as oviparous reptiles, birds, and mammals that exhibit various reproductive strategies such as induced ovarian maturation (for example, musk shrew), induced ovulation (for example, cats and ferrets), serial ovulation (for example, rabbits), or extended follicular phases (for example, carnivores and humans), the relationship between ovarian steroid secretion and the onset of sexual receptivity does not share the same temporal association with ovulation (Conaway 1971, Crews 1984). For example, the vitellogenic phase of the ovarian cycle of the parthenogenetic whiptail averages 9 days, during the latter stages of which individuals are receptive. Although it may be adaptive for female laboratory rats to become behaviorally insensitive to E2 in the hours following the initial E2 surge, species such as the whiptail lizard may need to increase neural sensitivity to E2 in response to the initial surge of E2 in the early stages of follicular growth.

Similarly, some mammals experience elevated E2 levels and display behavioral estrus for several days. In many carnivores, such as dogs, cats, and bears, behavioral estrus lasts over 1 week (Asa 1987). At the extreme are the serial ovulators, such as the rabbit, in which fe-

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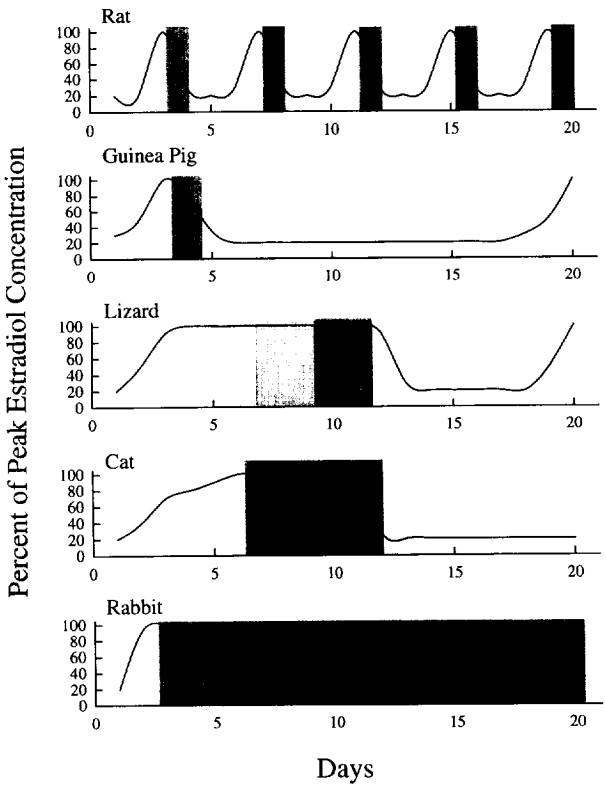


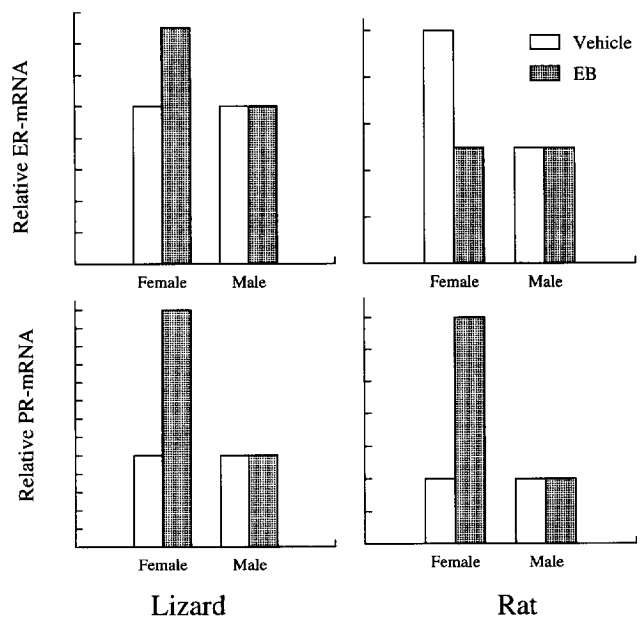
Figure 5. Relationship between circulating levels of ovarian hormones and sexual receptivity in several representative vertebrates. The species shown differ in the duration and frequency of their follicular phase as reflected in the circulating estradiol concentrations. The *shaded areas* represent the period of behavioral estrus. It is predicted that in species with extended or overlapping follicular phases and/or behavioral estrus, the estrogenic regulation of estrogen receptor-mRNA expression in the ventromedial nucleus of the hypothalamus would differ from that of the laboratory rat.

males are in constant estrus and E2, secreted by successive waves of developing follicles, remains elevated throughout the breeding season (see Figure 5). We predict that in other reptiles, as well as in birds and mammals like the rabbit and cat, E2 would upregulate ER gene expression in the VMH in a manner similar to that observed in whiptail lizards. Furthermore, in species with follicular cycles similar to that of the laboratory rat, E2 would downregulate ER synthesis in the VMH. There are, in fact, immunohistochemical data suggesting this to be the case in the guinea pig (Meredith et al. 1994).

Differences in sex steroid receptor gene expression and regulation can also be found between the sexes in sexually reproducing species. Although in the female laboratory rat, estrogen decreases ER gene expression and increases PR gene expression in the VMH, EB has no such effect in males (Lauber et al. 1991c). In the male whiptail lizard, EB increases both ER- and PR-mRNA expression in females, but has no effect in males (Figure 6) (Godwin and Crews 1995). Thus, although the regulation of ER in the VMH of laboratory rats and whiptail lizards is in opposite direction in females, sexual dimorphisms in regulation are phylogenetically conserved.

Some data on the sex steroid hormone regulation of sex steroid receptor expression must be interpreted with care. For example, estrogen activates the ER protein, changing the physical characteristics of the molecule (Truss and Beato 1993). In radioligand binding assays, this results in a decrease, or a downregulation, in the number of ER proteins in the "cytosolic" fraction of tissue homogenates. Immunocytochemical assays may also be affected by the activation of ER after estrogen treatment. For example, the commonly used ER antibody, H222, appears to have less affinity for the activated ER than the unoccupied form (Meredith et al. 1994). This results in an apparent, but artifactual, downregulation of ER protein following estrogen treatment. Therefore, techniques that measure mRNA synthesis, such as in situ hybridization, are better suited for investigating the regulation of sex ste-

Figure 6. Sex differences in the regulation of estrogen receptor (ER)-mRNA and progesterone receptor (PR)-mRNA expression by estradiol in the ventromedial nucleus of the hypothalamus of the laboratory rat and whiptail lizards. Notice that although the pattern of regulation of PR-mRNA expression is similar between the species, the regulation of ER-mRNA expression is in the opposite direction. In both instances, however, the sexual dimorphism remains. Graphs were generated based on data from Lauber et al. 1991c and Godwin and Crews 1995.



roid receptor synthesis by sex steroid hormones.

• Conservation in the Neuroanatomical Distribution of Sex Steroid Receptors

The highly conserved nature of sex steroid receptor distribution across species is useful in identifying homologous structures in divergent species. For example, in birds and squamate reptiles the dorsal ventricular ridge (DVR) processes visual, tactile, and auditory information and is thought to be homologous to the neocortex of mammals (Ulinski 1983). Neuroendocrine studies of birdsong have identified the magnocellular nucleus of the anterior neostriatum (MAN) in the DVR as involved in the androgen-dependent acquisition and production of song (Nottebohm 1980). Immunocytochemical and steroid autoradiography studies indicate that neurons in this region contain AR. Interestingly, whiptail lizards, which are not thought to vocalize, have a population of neurons that express AR in a similar region of the anterior DVR. This same region is known to process auditory information in gekkonid lizards (Marcellini 1977, Young et al. 1994). One possibility why whiptail lizards possess androgen responsive auditory nuclei is that they do vocalize. A more likely possibility is that the pattern of sex steroid hormone-concentrating neurons established in the ancient vertebrate brain may be so intricately related to developmental processes that it is difficult to change without somehow adversely affecting other developmental processes. If true, the pattern of sex steroid receptor gene expression in some brain regions may better reflect evolutionary history than present-day function.

Although the distribution of sex steroid hormone-concentrating neurons in evolutionarily ancient structures such as the limbic system appears to be fixed in the vertebrate brain, it has been suggested that sex steroid receptors in more recently evolved structures of the brain are more likely to exhibit species differences (Gahr et al. 1993). For example, songbirds possess a number of sex steroid hormone-sensitive structures involved in the acquisition and production of song (Gahr et al. 1987, Watson and Adkins-Regan 1989, Balthazart et al. 1992). A survey of ER immunoreactivity (ER-IR) in 26 avian species revealed a unique pattern of ER-IR in several nuclei involved in the control of song in songbirds compared with nonsongbirds, suggesting that species differences in the pattern of ER gene expression may be linked to species differences in behavior (Gahr et al. 1993).

• Conclusions

Comparative analysis indicates that although some aspects of the neuroendocrine mechanisms subserving reproductive behavior have remained relatively constant throughout vertebrate evolution, other aspects, such as the regulation of sex steroid receptor gene expression, are more plastic. Species differences in the circulating concentration of sex steroid hormones are likely to be related to differences in the sensitivity to sex steroid hormones, as well as the regulation of sex steroid receptor expression in specific regions of the brain. The contrasting regulation of ER expression in the hypothalamus in laboratory rats and whiptail lizards clearly demonstrates the flexibility in sex steroid receptor gene regulation and provides an example of the coordinated evolution of sex steroid receptor regulation and reproductive physiology. Finally, although the neuroanatomical distribution of sex steroid receptors is highly conserved among vertebrates, species differences in the neuroanatomical distribution of ER expression demonstrate that some flexibility exists in the tissue-specific expression of sex steroid receptor genes, and that this flexibility may play a role in the evolution of behavior. As more comparative data on the expression of genes coding for sex steroid receptors become available, we will gain a better understanding of the role of sex steroid receptors in the evolution and control of species-typical reproductive biology.

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