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Evolutionary Perspectives on Sex Steroids in the Vertebrates

Nigel C. Noriega
University of California at Davis,
Department of Neurobiology,
Physiology and Behavior
USA

1. Introduction

The term "sex-steroids" refers to estrogen, androgen and progestin products of vertebrate gonads. Sex steroids were so named for their influence on the sexually dimorphic development of the reproductive tract, secondary sex characters and central nervous system, which cause subsequent sexually dimorphic behavior and physiology (Phoenix et al. 1959b; Breedlove & Arnold 1983b). Receptors for sex-steroids are present in almost all tissues, and sex-steroids may be synthesized from cholesterol in the gonads, adrenals and brain. Although commonly described as endocrine components released into the bloodstream, sex-steroids may be generated through conversion from other (particularly adrenal) circulating steroids (Hinson et al. 2010) or generated de novo from cholesterol via intracrine pathways, as in the case of the brain neurosteroids (Baulieu 1997).

In this chapter we examine how sex-steroids fit into the larger themes of metazoan physiology and reproduction, and examine why these compounds may function the way they do in vertebrates. I aim to present broad concepts in a manner that is easily accessible to the non-specialized reader. It will be useful for the reader to be able to navigate modern versions of metazoan systematics. Therefore I aim to utilize the open-source nature of this publication by providing links that encourage the reader to use the Tree of Life web project (http://tolweb.org/tree/) for up-to-date "locations" of animals within the organization of living things. Navigation instructions for the Tree of Life web project are located at: (http://tolweb.org/tree/home.pages/navigating.html). In summary, clicking the leftward-pointing arrow on a given tree will navigate to the next broader category. Clicking text on the right side of the tree will navigate inside the highlighted group (the next narrower category).

2. Hormonal axes, gonadotropins and gonadotropin releasing hormones

In vertebrates, gonadal activity and steroid release are stimulated by members of a family of glycoprotein hormones known as gonadotropins. Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) typify the gonadotropins, which may be derived from multiple sources, but have highly conserved functionality across species. For example, chorionic gonadotropins (CG) are produced by primate fetus, placenta and pituitary gland (Cole 2009). The human chorionic gonadotropin (hCG) is an effective gonadotropin in amphibians

(Holland & Dumont 1975), fish (Targonska & Kucharczyk 2010) and reptiles (Arslan et al. 1977). This example is included to illustrate the conservative nature of gonadotropin function.
LH and FSH are released from the pituitary gland and regulated by Gonadotropin Releasing Hormone (GnRH) secreted from the hypothalamus of the brain. Several versions of GnRH also may be derived from multiple sources within the body, but the hypothalamus in the brain releases the organism-specific GnRH version that regulates gonadotropins. This control route: Hypothalamus → Pituitary → Gonad, is called the hypothalamic-pituitary-gonadal (HPG) axis, and is one of several highly conserved hypothalamic-pituitary-hormonal axes in the vertebrates.
The hypothalamus and pituitary operate under negative feedback control regulated by levels of gonadotropins and sex-steroids. These HPG axis feedback loops are in turn influenced by complex interactions between additional neurotransmitter and hormonal systems, which are themselves influenced by feedback from a vast array of additional hormones and signaling molecules (Williams & Larsen 2003; Oakley et al. 2009). Although the HPG axis is conceptually simple, it is one of several hubs in a network. This system is connected to other systems through complex interactive networks. The theme of interactive complexity is critical in modern considerations of endocrinology.
Reproduction is coordinated with growth and development, which is tied to metabolism. At the core of metabolic and developmental regulation is the Hypothalamic-Pituitary-Thyroid (HPT) axis. The pituitary gonadotropins (LH and FSH), thyroid stimulating hormone (TSH) as well as thyrostimulin (Nakabayashi et al. 2002) and chorionic gonadotropin (CG) are members of a family of heterodimeric glycoproteins (sharing a common α subunit but unique β subunits) which likely evolved from a common ancestral molecule (Kawauchi & Sower 2006). The discovery of thyrostimulin homologs in invertebrates suggests that this most ancestral heterodimeric glycoprotein hormone existed before the divergence of vertebrates and invertebrates (Sudo et al. 2005). This finding also supports hypotheses for the existence of early, overlapping yet functional HPG and HPT endocrine systems prior to extant vertebrates (Sower et al. 2009).

2.1 Separation of hormonal axes

Operating on similar principles of negative feedback inhibition, the hypothalamic-pituitary-gonadal (HPG) axis, the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal (HPA) axis target organs are gonads, thyroid gland and adrenal glands respectively. Pituitary glycoproteins are used in both the HPG and HPT axes, with luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the HPG axis and thyroid stimulating hormone (TSH) in the HPT axis. Although these axes appear separated in more derived vertebrates, they are less specified in evolutionarily older taxa. Agnathans (hagfishes and lampreys) are the oldest extant lineage of the vertebrates. The endocrine control of reproductive and thyroid functions in lamprey may reflect an intermediary stage on the evolutionary pathway to the highly specialized HPG and HPT axes currently observed in jawed vertebrates (gnathostoma: http://tolweb.org/Vertebrata) (Sower et al. 2009).

2.2 GnRH

Because the role of GnRH at the head of the HPG regulatory cascade is so highly conserved across vertebrates, GnRH has been referred to as the master molecule of reproduction. This master molecule acts in coordination with a host of other molecules. In order to facilitate this

coordination, hypothalamic GnRH neurons are influenced by over 30 neurotransmitters, neuropeptides cytokines, hormones and growth factors in the brain (Gore 2002).
GnRH binding sites have been detected in several regions of the mammalian brain (Jennes et al. 1997), testicular Leydig cells (Bourne et al. 1980), the placenta (Bramley et al. 1992), ovarian luteal and granulosa cells (Hazum & Nimrod 1982), adrenal cortex (Eidne et al. 1985), immune tissues including thymus (Marchetti et al. 1989), spleen, blood lymphocytes (Marchetti et al. 1998), and several other tissues (Gore 2002). Although the HPG function of GnRH is highly conserved, possible alternative roles for GnRH molecules are poorly understood and rarely investigated. For example, the prevalence of GnRH-II in the midbrain of most vertebrates and its association with sensory and motor functions implies that GnRH molecules may have been important neural regulators (Tsai & Zhang 2008). However, interruption of GnRH function produces sterility in all vertebrate classes, and the pattern of GnRH expression in brains across vertebrate classes is so ubiquitous that some authors have proposed the existence of GnRH "lineages" such as a conserved GnRH-II or mesencephalic lineage, and a hypothalamic or "releasing" lineage (Somoza et al. 2002).
Such ubiquity may be indicative of more generalized roles for GnRH in ancient organisms. The presence of multiple GnRH genes in all vertebrate classes, as well as the homology of functional GnRH peptides and receptors between vertebrates, and tunicates (compare Craniata and Urochordata in http://tolweb.org/Chordata/2499) indicate that GnRH genes were present before the evolution of vertebrates (Somoza et al. 2002). It is suggested that in ancestral chordates, before the evolution of the pituitary, GnRH was released from sinuses near the gonads into the bloodstream and acted directly on the gonads (Powell et al. 1996).
Because, GnRH molecules are small (10-15 peptides), diverse, and can serve multiple functions in the same organism, it is difficult to assess the significance or evolutionary directionality of single peptide changes in GnRH structure. The short length of these peptides also makes statistically rigorous sequence comparisons difficult, and raises questions as to whether GnRH genes in distant evolutionary lineages are the result of convergent evolution or orthologous genes. Despite these difficulties, phylogenetic analyses have elucidated relationships among the vertebrate GnRH peptides and receptors (Levavi-Sivan et al. 2010). The discovery of a receptor for octopus GnRH with sequence (Kanda et al. 2006) and functional similarity to vertebrate GnRH receptor (Millar et al. 2004) suggests that a common GnRH ancestor may have been shared between chordates and protostomes (Tsai & Zhang 2008). Even in modern times, various GnRH molecules show cross functionality between the protostomes and deuterostomes (Table 1).

2.3 System complexity: Sex-steroid coordination with other hormone systems

Dynamic changes in serum sex-steroid levels are associated with sexual behavior. This is accomplished through HPG coordination with other hormonal systems where metabolic regulators such as Polypeptide YY, ghrelin, glucose, insulin and leptin influence GnRH release (Fernandez-Fernandez et al. 2006; Gamba & Pralong 2006; Tena-Sempere 2008; Roland & Moenter 2011). Progesterone acts in coordination with estradiol to regulate female sexual receptivity in reptiles (Wu et al. 1985). Opiates modulate gonadotropin secretion in mammals (Brooks et al. 1986). Adrenal steroids such as corticosterone affect courtship behavior in amphibians (Moore & Miller 1984). What often appear to be effects of testosterone are mediated through the conversion of testosterone to other androgens or estrogens (Callard 1983).

Source taxon	Molecule	Effect	Recipient	Recipient taxon	Reference
cnidarian	GnRH (HPLC purified)	LH release	Sea porgy pituitary cells	fish	(Twan et al. 2006)
vertebrate	chicken GnRH-II*	Δ in neuronal discharge from reproductive cells	California sea slug	gastropod	(Zhang et al. 2000)
gastropod	GnRH (HPLC purified)	gonadotropin release	goldfish pituitary cells	fish	(Goldberg et al. 1993)
cephalopod	GnRH (HPLC purified)	LH release	quail pituitary cells	bird	(Iwakoshi et al. 2002)
mammal, bird, fish lamprey	GnRH (5 commercial preps)	[^{3}H]thymidine incorporation	*Crassostria gigas* gonial cells	bivalve	(Pazos & Mathieu 1999)
mammal	mammal GnRH	mitosis	*Mytilus edulis* mantle cells	bivalve	(Pazos & Mathieu 1999)
yeast	α-factor	LH release	rat pituitary cells	mammal	(Ciejek et al. 1977) (Loumaye et al. 1982)

Table 1. Examples showing GnRH cross functionality between organisms whose evolutionary divergence pre-dates the split between protostomes and deuterostomes.

The steroid hormone binding globulins (SHBG) form a third class of steroid binding protein in addition to nuclear and membrane bound receptors (Section 3), and are distinguished by their rapid dissociation constants (Pardridge 1987). Increased ligand specificity in more recently derived lineages indicates that SHBGs may have been important in the evolution of complex endocrine systems. For example, circulating steroid binding proteins appear scarce in the lampreys (Hyperoartia: http://tolweb.org/Vertebrata/14829) where an α1 globulin is specific to progesterone and a β globulin is specific to estradiol, but neither is specific to testosterone or corticosteroids. Chondrichthyes (http://tolweb.org/Gnathostomata/14843) show plasma SHBGs with generalized specificities for estradiol, testosterone, progesterone and corticosterone. In the osteichthyes, plasma SHBGs are more specific to estradiol and testosterone compared to progesterone and corticosterone (Bobe et al. 2010). In mammals (http://tolweb.org/Therapsida/14973), SHBGs regulate the accessibility of sex-steroids to various organs. For example, bound estradiol is unable to pass the blood brain barrier, whereas unbound testosterone has relatively high access to the brain (Pardridge et al. 1980). SHBGs may also bind environmental compounds that influence hormonal activity (Crain et al. 1998).

Prostaglandins act as local intra and inter-cellular regulators (Stacey 1987) that modulate gonadotropin release, ovulation and sexual behavior in vertebrates ranging from fish to mammals. The neurohypophysial peptide hormones released from the neural lobe of the pituitary act in coordination with steroids such as aldosterone and cortisol, as well as prolactin to regulate osmotic and fluid pressure (Nishimura 1985).

Kisspeptins are a family of neuropeptides expressed in the hypothalamus that act as important regulators of GnRH neuron activity and the HPG axis. Sex steroids directly influence kisspeptin neurons, which in turn directly influence GnRH neurons (Han et al. 2005; Pielecka-Fortuna & Moenter 2010). Other physiologically important molecules interacting with Kisspeptin neurons include neurokinin B (NKB), and dynorphin (Lehman et al. 2010), leptin, proopiomelanocortin (POMC), neuropeptide Y (NPY) (Backholer et al. 2010), and Gonadotropin Inhibiting Hormone (GnIH) (Smith et al. 2008). Kisspeptins are key

players in the integration of behavioral, maturational and metabolic feedback control of gonadotropins by sex-steroids (Norris & Lopez 2011a; Roa et al. 2011).

Using the variety of systems acting on the HPG axis, estrogen-mediated behavior, such as lordosis in sexually receptive rats, involves coordination of multiple steroid hormones, neuropeptides and prostaglandins (Sodersten et al. 1983; Sirinathsinghji 1984). Similarly, sexual behavior of the male rough-skinned newt *Taricha granulosa* is regulated by complex endocrine coordination of GnRH-regulated androgenic and estrogenic sex-steroids (Moore 1978; Moore & Miller 1983) together with GnRH, arginine vasotocin (AVT), and melanocyte stimulating hormone (MSH), as well HPA axis components; adrenocorticotropic hormone (ACTH), corticotropin releasing factor (CRF) and the adrenal steroid corticosterone (Moore et al. 1982; Moore & Miller 1984).

The evolution of complex coordination may offer finer appropriation of sex-steroid mediated behavioral responses to complex, nuanced or varied stimuli, and may allow robustness of important behaviors when uncoupled from what may once have been key regulators (Crews & Moore 1986; Moore 1987). For example, sexual behaviors of male garter snakes and white-crowned sparrows occur in the absence of plasma testosterone (Moore & Kranz 1983; Crews et al. 1984) although testicular androgens still regulate male secondary sex characters in these species (Crews et al. 1985). Such interactive complexity allows for the sex-specific evolution of environmentally and socially contingent use of sex-steroids within members of the same species. Interactive complexity may be a means by which diversity of behavioral modes involving olfactory, tactile, visual, auditory, photoperiodic, nutritional, habitat selection and conspecific display cues affecting fertility and fitness evolved in vertebrates (Crews 1987b).

3. Before the vertebrates: Sex steroids in the bilaterian animal lineages (Bilateria: http://tolweb.org/Animals/2374)

3.1 Steroids in evolution

Steroid and thyroid hormones were originally thought to bind only to receptors found in the cell nucleus, where effects were exerted via gene transcription. We now know that in addition to binding to nuclear receptors, estrogens also illicit rapid non-genomic responses via membrane bound receptors (Pietras & Szego 1977). The nuclear receptors are grouped in a superfamily of ligand-activated transcription factors (Whitfield et al. 1999; Robinson-Rechavi et al. 2003) which are specific to animals (http://tolweb.org/Animals) and bind compounds such as steroids, thyroid hormones, and retinoids (Bertrand et al. 2004). Because steroids are lipids, their structures provide little phylogenetic information. However, we can examine the evolution of steroid receptors because they are proteins encoded by genes. Construction of a truly reliable animal phylogenetic tree is currently a difficult objective because expansion of techniques across molecular, developmental and evolutionary biology, as well continued discoveries of new taxa reveal common secondary simplifications of morphology and developmental processes that repeatedly challenge the validity of assumptions that evolution proceeds from simple to more complex (Telford & Littlewood 2009). The converse, that rapid evolution is associated with simplification, may be just as well founded. When using extant species for evolutionary clues, it must be noted that groups like ascidians (urochordates: http://tolweb.org/Chordata/2499), nematodes (in Ecdyzoa: http://tolweb.org/Bilateria/2459), and acoel flatworms (in Platyhelminthes:

http://tolweb.org/Bilateria/2459) are characterized by high rates of molecular evolution that can lead to large amounts of secondary gene loss (Ruiz-Trillo et al. 1999; Hughes & Friedman 2005).

Steroid receptors evolved in two main branches from an ancestral steroid receptor (ancSR1) that was likely to be estrogen-activated (Thornton et al. 2003) (Figure 1). One branch contains the estrogen receptors (ER) and is descended from ancSR1. The other branch likely evolved from a gene duplication of the original ancSR1. This duplicate gave rise to an ancSR2 which was altered to bind 3-ketosteroids. This 3-ketosteroid receptor group derived from ancSR2 contains diversified steroid receptors for androgens (AR); progestins (PR); glucocorticoids (GR); and mineralocorticoids (MR) (Schwabe & Teichmann). Only representatives of the ER branch have been detected in fully sequenced genomes of molluscs and annelids (both in Lophotrochozoa: http://tolweb.org/Bilateria/2459) (Eick & Thornton 2011). However, the lancelets (cephalochordate: http://tolweb.org/Chordata/2499) contain two steroid receptors, one from the ER branch and one possibly derived from the 3-ketosteroid receptor (AR/GR/MR/PR) branch (Bridgham et al. 2008; Katsu et al. 2010).

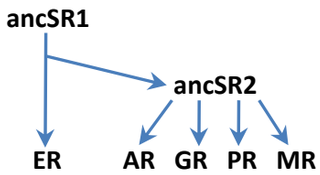

Fig. 1. Simplified schematic of proposed steroid receptor evolution (Thornton et al. 2003). ancSR = ancestral steroid receptor; AR = androgen receptor; ER = estrogen receptor; GR = glucocorticoid receptor; PR = progesterone receptor; MR = mineralocorticoid receptor.

3.2 Estrogen receptors in animal evolution

Estrogen receptor (ER) orthologs have recently been discovered in well-known molluscs: *Aplysia californica* (California sea slug) and *Octopus vulgaris* (the common octopus), as well as annelid marine polychaete worms, *Platynereis dumerilii* and *Capitella capitata* (Lophotrochozoa: http://tolweb.org/Bilateria/2459). All of these organisms are protostomes, indicating that the ancestral steroid receptor was likely present before the separation between protostomes and deuterostomes. This evidence supports the hypothesis that the ER was secondarily lost in taxa such as arthropod and nematode protostomes (Maglich et al. 2001), or the urochordate and echinoderm deuterostomes where definitive orthologs have not been detected (reviewed in Eick & Thornton (2011).

Care is suggested for interpreting the steroidogenic potential of GnRH molecules in molluscs (Tsai & Zhang 2008). This is because the estrogen receptor (ER) orthologs for molluscs like the California sea slug, common octopus, pacific oyster *Crassostrea gigas* and the marine snail *Thais clavigera* are constitutively active and unresponsive to estrogens or other vertebrate steroid hormones (Thornton et al. 2003; Kajiwara et al. 2006; Keay et al. 2006; Matsumoto et al. 2007).

3.3 Androgens and progestins

In early animals, more generalized versions of the roles we currently associate with sex-steroids may have been assigned to alternative compounds. Steroids which at one point

were intermediate compounds in the synthesis of ligands for a particular receptor, may have become ligands for alternative "orphan" receptors (Thornton 2001).
Steroid receptors for androgens (AR) and progestins (PR) likely arose out of adaptations for specialized endocrine systems through such use of intermediary steroid metabolites (Eick & Thornton 2011).
For example, the agnathans (lampreys and hagfish in Craniata: http://tolweb.org/Chordata/2499) may be illustrative of the evolutionary stage before gene duplication of the original ER-like ancSR1 generated ancSR2. Remember that ancSR2 (section 3.1) is believed to be ancestral to the modern 3-ketosteroid receptor (AR/GR/MR/PR) family (Thornton 2001; Thornton et al. 2003). An example of evidence for this hypothesis is that in the European river lamprey, (*Lampetra fluviatilis*) and the arctic/Japanese lamprey (*Lampetra japonica*), testosterone concentrations range from low to non-detectable, and do not seem correlated to life stage or gender (Fukayama & Takahashi 1985; Klime & Larsen 1987). However, androstenedione (an androgen), is responsive to GnRH (see below) and acts as a hormone, increasing the development of secondary sex characteristics and accelerating maturation in sea lampreys (*Petromyzon marinus*) (Bryan et al. 2007). These findings are significant because androstenedione is an androgenic precursor in vertebrates, but in lampreys, GnRH may be eliciting release of steroids for much less specific steroid receptor binding than we see in animals with more complex endocrine systems. Additional support for this hypothesis comes from observations that progesterone and estradiol have been detected in sea lamprey plasma of both sexes, and concentrations of both of these hormones change in response to GnRH stimulation (Gazourian et al. 1997).

3.4 The noteworthy case of the octopus

The common octopus, *Octopus vulgaris*, is the first invertebrate species shown to possess representatives of three classes of sex-steroids found in vertebrates (progestins, androgens and estrogens) as well as binding proteins for these steroids (Di Cosmo et al. 2001). The octopus also possesses a progesterone receptor (Di Cosmo et al. 1998) and an estrogen receptor (Di Cosmo et al. 2002). Another vertebrate-like trait of the octopus is the expression of two peptides belonging to the oxytocin/vasopressin superfamily (Kanda et al. 2005) as well as associated receptors for one such peptide (Kanda et al. 2003). In addition, enzymatic (3beta-Hydroxysteroid dehydrogenase) activity has been detected in the ovary, indicating that the octopus reproductive system is a source of steroidogenesis (Di Cosmo et al. 2001). These findings display an astonishing level of functional parallelism with vertebrates, especially in consideration of the vast evolutionary distance between cephalopods (mollusca) and gnathostomes (deuterostomia) among the bilateria (http://tolweb.org/Bilateria/2459). These findings further support the hypothesis that secondary loss of ancestral steroid receptor function occurred in the arthropod and nematode protostomes, as well as urochordate and echinoderm deuterostomes (Maglich et al. 2001; Eick & Thornton 2011).

4. Reproductive variability among the vertebrate classes (http://tolweb.org/Gnathostomata/14843)

Sex steroids were largely characterized based on their roles in sex-determination and sex-differentiation as described for gonochoristic species. These are species with two sexes (male

and female) where once the sex of an individual is determined, the individual differentiates into that sex only once during its lifetime. Mechanisms of sex determination are characterized as genetic, temperature-dependent, and behavioral (Crews 1993). Sex steroids are integral to sex-specific differentiation of the reproductive tracts and development of corresponding secondary sex characteristics and behaviors in all vertebrate groups (Norris & Lopez 2011a). In many fish species, an individual may normally undergo sex differentiation on multiple occasions during a lifetime (Thresher 1984). The spectrum of reproductive strategies utilized by vertebrates (Figure 2) is illustrative of the variety of sex-steroid mediated behavioral and physiological modifications that are feasible (Lombardi 1998; Norris & Lopez 2011a).

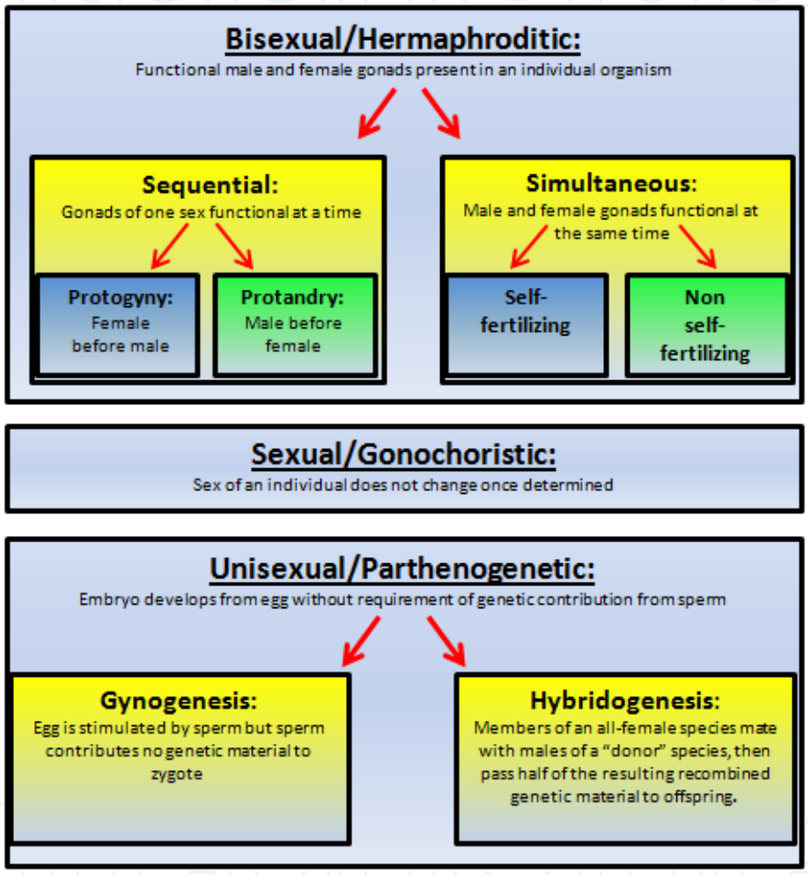

Fig. 2. Summary of vertebrate reproductive strategies (Harrington 1961; Schultz 1973) (Charnov et al. 1976; Potts et al. 1984; Crews 1987b; Paul-Prasanth et al. 2011).

4.1 Fishes

Living members of fishes include the Sarcopteriygii, Actinopterygii and Chondrichthyes of the jawed vertebrates (http://tolweb.org/Gnathostomata/14843). Fishes include groups that show a faster evolution of protein sequences and conserved noncoding elements than mammals, and some of the highest "evolvability" observed in vertebrates (Ravi & Venkatesh 2008)

Fish also exhibit the highest degree of reproductive plasticity and diversity of strategies observed in vertebrates (Potts et al. 1984; Crews 1987b; Paul-Prasanth et al. 2011). Often,

combinations of sex-determining mechanisms are observed in a single species, such as the internally self-fertilizing bisexual cyprinodont *Rivulus marmoratus*, in which both temperature-dependent and genetic sex-determining mechanisms are utilized (Harrington 1961; Harrington & Crossman 1976). Sex reversal and sequential hermaphroditism is well described (Shapiro 1984) in many species of reef fishes. Sex changing fish can perform both male-typical and female-typical sexual behaviors and functions during a single lifetime. Functional sex reversal can also be induced with hormonal treatment in fish that do not normally undergo sex change.

Many fish species have multiple male phenotypes where each phenotype makes different types of investments in reproduction. Each of these types of males requires different endocrine settings as well as neuroendocrine and behavioral parameters. The theme of two types of males within a species becomes more complicated when considering sex-changing reef fishes such as wrasses and parrotfish. Here the "primary" males are small with female like coloration, and sneak in on spawning aggregations or the matings of secondary (terminal) males. Terminal males are large and brightly colored, and maintain territories. The development of terminal males varies according to species, and may occur through transformation of primary males as well as through sex change of a female (Warner 1982).

Sex change in fishes can be induced by social conditions and relative size of neighboring conspecifics (Thresher 1984; Warner 1984). Sex change may also be initiated through application of exogenous testosterone (Chan & Yeung 1983; Kramer et al. 1988). Rapid color changes observed in sex-changing fish involve integration of visual stimuli with sex-steroid and GnRH action (Demski 1987).

4.2 Amphibians (http://tolweb.org/Amphibia)

Body compartmentalization adaptations necessary for transitioning from aquatic to terrestrial life are abundant in amphibians. Both genetic and temperature-dependent mechanisms may interact to influence sex determination in this clade (Nakamura 2009; 2010). Although the naturally occurring range of observed developmental plasticity is narrower than in fishes, many amphibians can be sex-reversed with sex-steroid application. For example, estrogen effects on gonadal differentiation range from masculinization to feminization, and vary widely according to species, administration protocol, and interactions with other steroids (Hayes 1997b). Much of this variation may be related to the physiological stage of the animal at the time of exposure (reviewed in Hayes (1998). Sex steroid effects on amphibian rates of metamorphosis (Sluczewski & Roth 1950) as well as adrenal steroid effects on courtship behavior (Moore & Miller 1984) and gonadal differentiation (Hayes 1998) are reflective of high levels of cross-connectivity between HPG, HPA and HPT systems (Hayes et al. 1993). Developmental timing can vary dramatically between closely related species (Buchholz & Hayes 2000), and differences in developmental timing may affect ages or stages when animals have achieved the organizational capacity to exhibit hormone-induced effects (Hayes 1997a).

Sex-steroids exert their most potent effects on sexual differentiation only during specific stages of development (Chang & Witschi 1956; Villalpando & Merchant-Larios 1990). This theme of "critical windows" of development is common in the vertebrates. It is an important consideration in evaluations of sex-steroid effects as well as effects of non-steroidal compounds such as atrazine (Hayes et al. 2002) or o,p'DDT (Noriega & Hayes 2000) which affect sex-steroid mediated development of primary and secondary sex characters.

4.3 Reptiles (Compare testudines and diapsida in: http://tolweb.org/Amniota/14990)

Reptilian use of sex-steroids shows the greatest diversity of sexual differentiation modes observed among extant amniotes. Temperature sex determination is observed in all crocodilians (Crocodylomorpha: http://tolweb.org/Archosauria/14900) examined (Deeming & Ferguson 1989), many chelonians and some squamates (Bull 1980). It is in the reptiles that we see the beginnings of mutual exclusivity between genetically determined sex and temperature determined sex (Bull 1980). Studies in reptiles have clarified that genetic and temperature dependent sex determining mechanisms operate along much more of a continuum than was originally perceived (Norris & Lopez 2011b). Of the 80 or so vertebrate taxa displaying unisexual reproduction, squamate reptiles are the only vertebrates shown to reproduce entirely in the absence of males (Kearney et al. 2009) (Neaves & Baumann 2011). Variations in sex-steroid levels appear to underlie behavioral and morphological differences among males with differences in functional roles such as "sneaker" vs. "territorial" or males displaying one color type vs. another (Norris & Lopez 2011b).

Well studied examples include several all-female parthenogenetic species of whiptail lizards (*Cnemidophorus*) secondarily evolved from sexual species which display male courtship behavior, but no such behavior between females (Cuellar 1977). In the all-female parthenogens, females have adopted displays of courtship and copulatory behavior that are identical to those of males from the ancestral species. This pseudomale copulatory behavior is not essential for reproduction (Cuellar 1971), but does increase fecundity (Crews & Fitzgerald 1980). In addition to pseudomale copulatory behavior, there are instances in gonochoristic species where courtship behavior is required for reproduction but does not lead to fertilization. These scenarios lend credence to hypotheses that copulatory behavior may be used to facilitate sociality as well as to deliver environmental or conditional cues important for overall fitness (Crews 1982; Crews & Moore 1986).

Female red-sided garter snakes *Thamnophis sirtalis* release an estrogen-dependent pheromone that attracts male garter snakes. Typical males do not express the female pheromone, but a subset of "she-males" release a similar or identical attractant as the females. "She-males" are genetic males with typical male morphology, and are able to achieve high mating success by using their pheromone release to lure typical males away before returning to mate with the then unattended females (Mason & Crews 1985). Males receiving exogenous estrogen produce the female pheromone (Garstka & Crews 1981), and estrogen administered to neonatal males causes them to be courted by adult males (Crews 1985). "She-males" have high circulating testosterone concentrations although estrogen concentrations are comparable to typical males, and it is hypothesized that aromatic conversion of testosterone to estrogens may be important for "she-male" pheromone production (Crews 1987a).

4.4 Birds (http://tolweb.org/Aves/15721)

In birds, temperature sex determination appears to have been lost, although it is still ubiquitous in the other living archosaur group (http://tolweb.org/Archosauria/14900), the crocodilians (Deeming & Ferguson 1989). One interesting exception is the case of the Australian brush-turkey (*Alectura lathami*), a member of the megapodes, a family which builds mound nests that are ambiently incubated in a manner reminiscent of crocodilians. Sex ratios in hatchling *A. lathami* are influenced by incubation temperature (Goth & Booth 2005). Birds are functionally gonochoristic. There are occasional reports of viable male

offspring from unfertilized eggs (Olsen & Marsden 1954; Sarvella 1974), but parthenogenesis does not seem to be currently used as a reproductive strategy in birds.

Compared to the reptiles, amphibians and fishes, reproductive strategies in birds are conservative. The overall chromosomal sex determination appears uniform, where females (ZW) are heterogametic and males (ZZ) are homogametic, resulting in a "default" male phenotype which occurs in the absence of endocrine influence (Mittwoch 1971; Adkins 1975; 1976; Elbrecht & Smith 1992). The ZZ/ZW female heterogametic sex determination system is opposite to the XX/XY male heterogametic scheme employed by mammals (section 4.5). In birds, conversion of testosterone to estrogen during critical windows of development (section 5) is required for demasculinization and feminization in the normal sexual differentiation of the female. Blockage of this conversion results in genetic females exhibiting male secondary sex characteristics and behavior (Elbrecht & Smith 1992).

Sex-steroids link the physiology of sexual differentiation, sexually dimorphic behavior, seasonality, parental care and brain changes related to song development (Norris & Lopez 2011c). In species where males provide significant parental care, plasma testosterone is kept at minimal levels needed to maintain the gonads, secondary sex characteristics and territorial behavior without interfering with expression of parental behavior (Wingfield & Moore 1987). In white-crowned and golden-crowned sparrows, photoperiodic cues influence levels of gonadal androgens in both sexes to affect appetite control centers of the brain in coordination with migration. Sex-steroids synchronize courtship behavior and reproductive status with seasonal environmental cues (Ramenofsky 2011).

4.5 Mammals (http://tolweb.org/Mammalia)

Mammals are a gonochoristic group using an XX/XY male heterogametic sex determination scheme where temperature sex determination appears to have been lost. In contrast to birds, the "default" sexual morphology is that of the homogametic female (XX), and androgens during critical windows of development (section 5) are required to defeminize and masculinize the default female morphology in order to generate a normal male morphology. However, deviations from the norm provide some of the most fascinating insights into the endocrinology of sex steroids. Spotted hyenas *Crocuta crocuta* represent an interesting paradox where females show a physical appearance and some behaviors that are more masculinized than males. Females have masculinized external genitalia, no external vaginal opening and give birth though a large pseudopenis. Female masculinization is evident at birth and maintained throughout life (Neaves et al. 1980; Frank et al. 1990). This masculinization of females is due to high levels of androgens originating from the adrenals and ovaries where steroidogenic pathways are altered compared to ovaries of typical placental mammals (Lindeque et al. 1986; Glickman et al. 1992). In addition, the placenta converts ovarian androstenedione to testosterone (Licht et al. 1992; Yalcinkaya et al. 1993).

Interactions between behavior, signaling molecules, HPA and HPG axes and the comparative evolution of complexity in endocrine systems across many species are well described in mammals (Park & Rissman 2011; Uphouse 2011). For example, the role of sex-steroids in parturition is peripheral to influences from prostaglandins in the marsupial tammar wallaby (*Macropus eugenii*) (http://tolweb.org/Marsupialia/15994). However, a coordinated interplay between fetal and maternal estrogens and progestins as well as the fetal HPA axis and placental hormones is observed in primates (http://tolweb.org/Primates/15963) (Young et al. 2011).

5. Applied considerations

With respect to ontogenetic development of sexual dimorphism in individuals, the effects of sex-steroids are commonly discussed using the "organizational" vs. "activational" nomenclature (Phoenix et al. 1959b; a; Arnold & Breedlove 1985). For a given structure, "organizational" typically refers to effects of sex-steroid exposure during a critical time window in early development which determines the type of response or morphology that the affected structure will have. "Activational" refers to acute effects of sex-steroids on the structure after the critical window during which the structure was organized (Whalen & Edwards 1967). The type of activation is dependent on the organizational effect that occurred during the critical window of development (Guillette et al. 1995).

5.1 Brain dimorphism

Naturally occurring dramatic sexual dimorphism in vertebrate brains are exemplified in canaries (*Serinus canaria*) and zebra finches (*Taeniopygia guttata*) where three vocal control areas in the brain are strikingly larger in males (Nottebohm & Arnold 1976). Sex steroid effects on sexually dimorphic brain development was originally investigated in mammals (Raisman & Field 1973) and have since been described in the broader central nervous system (Breedlove & Arnold 1983b; a) for all vertebrate classes (Norris & Lopez 2011a). Correspondingly, sexual dimorphisms of brain neurotransmitter systems are also now evident (De Vries et al. 1984) (Simerly et al. 1985). Note that while this classical view of sex-steroid involvement in the dimorphic brain development is very robust, the paradigm has shifted to incorporate sex differences due to gene expression which occur before gonadal differentiation and subsequent organizational effects of sex-steroids (Mccarthy & Arnold 2007; Arnold 2009).

6. The "endocrine disruptor" hypothesis

Organisms encounter many environmental compounds that approximate, diminish or enhance the activity of sex-steroids. As explained in the sections on fish and amphibians, exposure to sex-steroids can morphologically and functionally reverse the sex of many vertebrate species. Here, a brief history of subsets of key events characterizing the development and expansion of the endocrine disruptor hypothesis is outlined. Emphasis is placed on the types of compounds that have received attention due to their observed effectiveness, abundance or distribution in this regard. Arguments in this section are also described with reference to some of the hormone-treatment experiments leading to current perspectives regarding the endocrine disruption of normal reproductive behavior, development and function in wildlife and laboratory species.

Naturally-occurring compounds as well as anthropogenic compounds released into the environment due to human activity have been hypothesized to affect endocrine function in vertebrates by mimicking the action of endogenous hormones (Colborn & Clement 1992), thereby 'disrupting' normal endocrine settings. In cases of endocrine disruption, exposure levels are typically too low to have toxic or acute effects on adults (Colborn et al. 1993), but affect organisms during critical organizational periods of early life stages (Guillette et al. 1995). Tissue contaminant levels previously considered safe are sufficient to alter endogenous chemical mediation in fish (Sumpter & Jobling 1995; Jobling et al. 2006), amphibians (Hayes et al. 2002; Hayes et al. 2006; Hayes et al. 2010), reptiles (Crews et al. 1995; Guillette et al. 2000), birds (Ottinger et al. 2009), and mammals (Colborn et al. 1993).

Pasture-specific variations in plant-derived estrogens (Walker & Janney 1930) affect livestock fertility according to grazing location. Hormones and hormone analogs are routinely used to manage production of agricultural animals (Brooks et al. 1986) and byproducts of steroid analogs used in livestock production have endocrine activity and are likely to affect wildlife (Orlando et al. 2004; Soto et al. 2004; Durhan et al. 2006). Sex-steroids or their analogs are routinely applied in aquaculture and agriculture to manipulate the sex ratios, behavior and physiology of commercially reared vertebrates.

Metabolites of steroids applied to livestock have biological activity that may affect animals at sites removed from the source of application (Shelton 1990; Lone 1997; Meyer 2001). Similarly, effluent from pulp mills, paper mills and sewage treatment plants affecting the endocrinology of aquatic vertebrates are transported far from sites of entry into the environment (Jobling & Tyler 2003a; b).

A key feature in the development of the endocrine disruptor hypothesis was the concept of "environmental estrogens". The environmental estrogen was a hallmark of the hypothesis because estrogenic properties of the compounds first identified as endocrine disruptors were well described. For example, widespread use of the synthetic estrogen diethylstilbestrol (DES) in humans (Morrell 1941; Smith & Smith 1949b; a) continues to be one of the most well studied examples of endocrine disruption where effects in the exposed mothers are minimal compared to effects in their offspring who were exposed during critical windows of development (Giusti et al. 1995). Organochlorine pesticides and environmentally persistent chlorinated hydrocarbons designed to be harmless to exposed vertebrates tended to bioaccumulate and affect offspring of exposed animals. Key players in the environmental estrogen story included the synthetic estrogen DES; the organochlorine pesticides, DDT and methoxychlor; a host of polychlorinated biphenyls (PCB's); and the plasticizers bisphenol-A, nonylphenol, and octylphenol. Compounds of concern were identified based partially on their ability to bind to nuclear estrogen receptors (Blair et al. 2000), and activity observed using *in vivo* biological assessments of estrogen activity such as the rat uterotropic assay (Gray et al. 2004), and production of the egg yolk protein vitellogenin (Sumpter & Jobling 1995). *In vitro* induction of estrogen-responsive breast cancer cell lines (Klotz et al. 1996) and tests of transcription in response to estrogen receptor binding (Ernst et al. 1991) were also primary means of screening compounds for estrogenic activity. With mechanistic knowledge came distinctions between feminizing and demasculinizing effects, and the concept of anti-androgens were more carefully considered (Wilson et al. 2008) in addition to estrogens or anti-estrogens. Key anti-androgens were originally characterized by their antagonism of androgen receptor (AR). Further characterization was based on extensive batteries of *in vivo* reproductive tract and secondary sex character examinations in the laboratory rat. In these studies, androgen action *in utero*, or on pubertal development were examined (Gray et al. 2004; Owens et al. 2007). Recognized antiandrogens fell into classes including dicarboximide (Gray et al. 1994; Kelce & Wilson 1997) and imidazole fungicides (Vinggaard et al. 2002; Noriega et al. 2005), organochlorine insecticides (Kelce et al. 1995), urea-based herbicides (Gray et al. 1999; Lambright et al. 2000), phthalate esters used as plasticizers (Parks et al. 2000; Howdeshell et al. 2007), and polybrominated diphenyl ethers (PBDEs) used as flame retardants (Stoker et al. 2005).

Natural hormones (Stumm-Zollinger & Fair 1965) and birth control agents (Tabak et al. 1981) occurring in wastewater prompted concern over sewage effluents. Some compounds, such as the phthalate esters, diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP) and benzylbutyl phthalate (BBP), originally considered estrogenic (Jobling et al. 1995), also exhibited anti-androgenic properties by decreasing testosterone production in fetal testes

and reducing the expression of steroidogenic genes after *in utero* exposure (Parks et al. 2000; Wilson et al. 2004).

Although effects of endocrine disruptors are well documented, as explained earlier in the chapter, complex endocrine interactions with other steroids, peptides and lipids are integral to the function of sex-steroids in living vertebrates. Therefore it is critical to consider the enormous range of physiological variation that occurs in vertebrates under "normal" conditions that would be considered "uncontaminated" (Orlando & Guillette 2007). Using terms like "estrogenic" or "androgenic" may limit the scope of investigation because androgens and estrogens have well-characterized function in a very small percentage of species. In addition, phylogenetic assessments discussed earlier in this chapter may expand the scope of sex-steroid considerations outside of the vertebrates. For example, the recently characterized ER in molluscs is not responsive to steroid ligands (Thornton et al. 2003) (Keay et al. 2006; Matsumoto et al. 2007) and the cephalochordate ER acts as a constitutive repressor of estrogen response element (ERE) function (Bridgham et al. 2008; Paris et al. 2008). It is important to note that although compounds may be defined based on a given outcome or mechanism of action, almost all chemicals influence multiple physiological systems and influence the way physiological systems interact with each other. For example, compounds such as linuron (a urea-based herbicide) and prochloraz (an imidazole fungicide) act as anti-androgens via multiple mechanisms of action (Lambright et al. 2000; Wilson et al. 2004; Noriega et al. 2005).

6.1 A case study using prochloraz

Any number of compounds can be used to demonstrate endocrine disruption via an endocrine active chemical (EAC). However, prochloraz provides a highly illustrative example because it affects development of external mammalian genitalia with which readers will have prior familiarity. Much of the reason that an imidazole fungicides like prochloraz kill fungi is because they affect members of the diverse cytochrome P450 enzyme family (Mason et al. 1987; Riviere & Papich 2009), a group of enzymes catalyzing electron transfer in representatives of all classes of cellular life (Nebert et al. 1989; Lewis et al. 1998; De Mot & Parret 2002; Nelson 2011). These enzymes have been evolutionarily co-opted for vertebrate steroidogenesis, as well as the metabolism of steroids and xenobiotics (Gibson et al. 2002). In addition to affecting steroidogenic cytochrome P450 enzymes and reducing androgen production, prochloraz is an androgen receptor antagonist (Vinggaard et al. 2002; Noriega et al. 2005) and inhibits testicular expression for insulin-like hormone 3 (insl3), which affects gubernacular development (Wilson et al. 2004). An example of laboratory-administered *in utero* prochloraz exposure (Noriega et al. 2005) can be used for a discussion on effects of a non-steroidal compound on sex-steroid action as viewed throughout the historical development of the endocrine disruptor hypothesis. Namely:

1. Exposure (ingestion) over a time course (5 days) and dosage that produced no observable effects on directly exposed mothers, was sufficient to produce severe abnormalities in offspring of those mothers (figure 3) through secondary *in utero* exposure during critical windows for sex-steroid sensitive development;
2. Abnormalities such as vaginal morphology in males (figure 4), that might have initially been classified as "feminization" in the early history of the field are more accurately described as extreme cases of de-masculinization towards a default female morphology for the species in question.

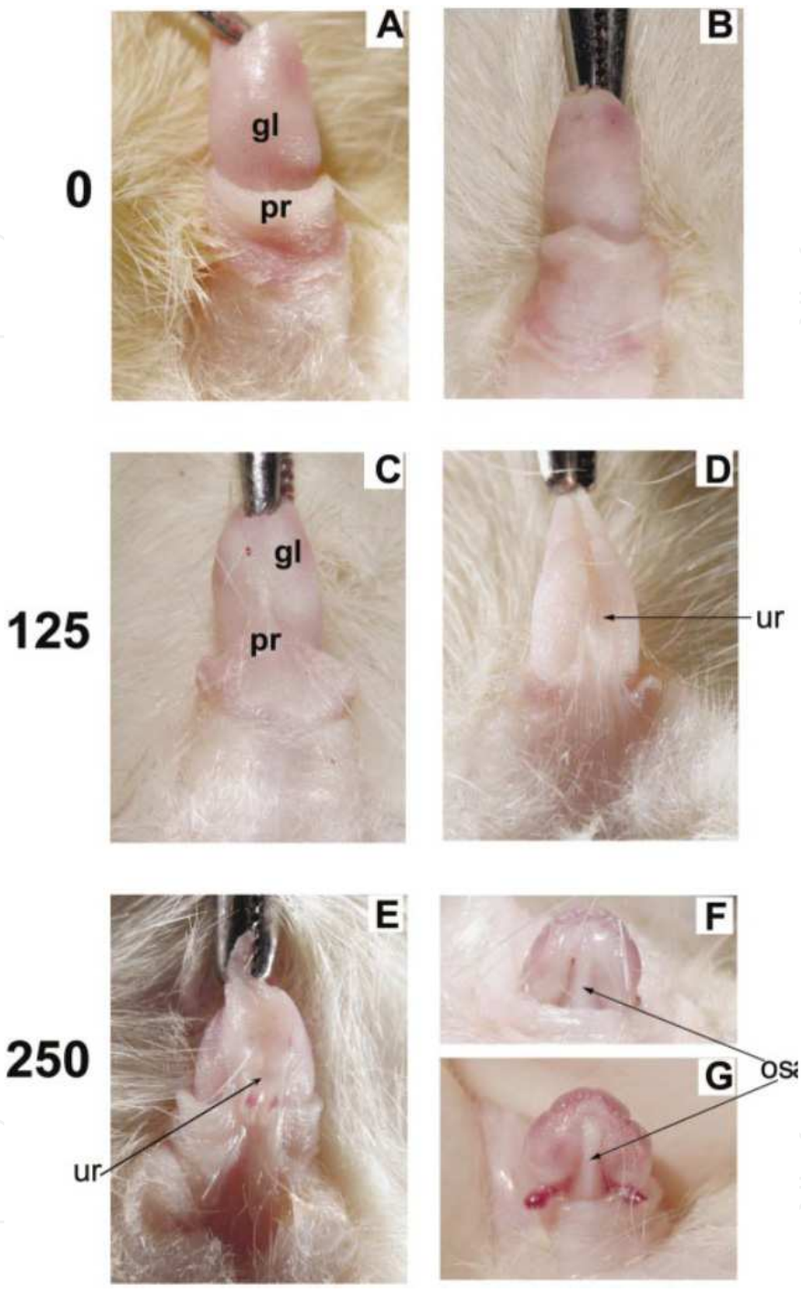

Fig. 3. Phallus abnormalities in adult male rats receiving a 5-day *in utero* exposure to prochloraz. Panels are arranged from left to right according to dosage group indicated by numbers to the left of the diagram. **A** and **B**) Variation within controls. **C** and **D**) Animals with a maternal dose of 125 mg/kg per day. **E–G**) Animals with a maternal dose of 250 mg/kg per day. gl, glans penis; pr, prepuce; ur, urethral opening; os, os penis. Hypospadias is evident in the two highest dosage groups and (**C–E**) show examples of incomplete preputial separation. Severe phallus clefting and exposure of the os penis is evident in the highest dosage group (**F** and **G**). (Noriega et al. 2005) modified with permission from the Society for the Study of Reproduction.

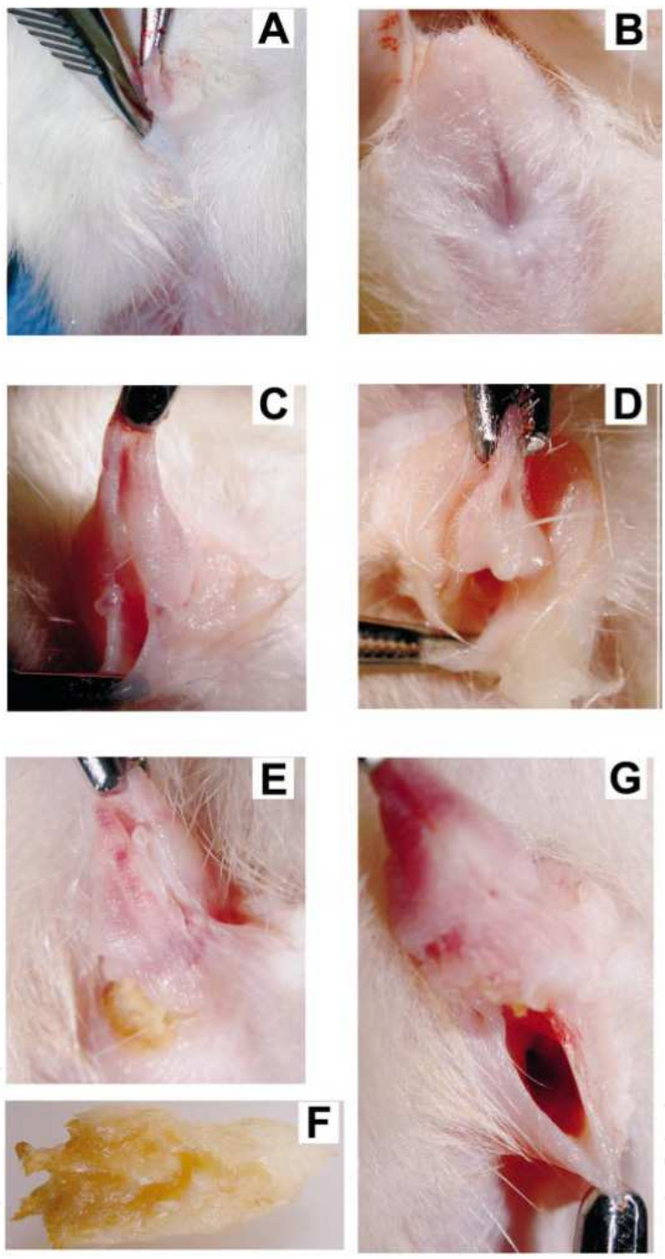

Fig. 4. Prochloraz-induced vaginal morphology in adult male rats receiving a 5-day *in utero* exposure. **A**) Panoramic view of a vaginal pouch (forceps inserted) in a male from the 250 mg/kg maternal dosage group. **B**) A close-up of a control female phallus and vaginal opening. **C** and **D**) Vaginal pouch and phallus deformity variations in males from the 250 mg/kg maternal dose group. **E–G**) The most severely affected animal from the 125 mg/kg maternal dose group. In this male, an ejaculatory plug (**F**) was found embedded (**E**) in the vaginal opening (**G**). (Noriega et al. 2005) modified with permission from the Society for the Study of Reproduction.

7. Conclusion

The terminology used in discussions of endocrinology, evolution and behavior is changing in light of the growing body of knowledge regarding the complexity of hormonal interactions. This chapter is intended to provide the reader with a panoramic snapshot of sex-steroid function compared to what is normally encountered in specialized fields of study. The summaries of concepts presented here will hopefully be catalysts for further investigation of topics in more detail than presented here. Existing paradigms regarding "disruption", "variation" and "adaptation" are increasingly seen as parts of a continuum. Thus the scope of "endocrine disruptor" assessment has already expanded beyond currently established definition parameters (Guillette 2006; Marty et al. 2011; Norris & Lopez 2011a). For example, the term "Endocrine Active Chemical" (EAC) is now used in favor of terms implying "disruption" (Norris & Lopez 2011a).

The claim has long been made that distinctions such as endocrine system vs. nervous system are arbitrary (Roth et al. 1986). Evolutionary constraints lead to reduced variation in reproductive strategies used by birds and mammals compared to evolutionarily older clades represented by fishes, reptiles and amphibians. However, the evolution of complex neuroendocrine systems may provide time and context-specific behavioral avenues for adaptive radiation in the face of external influences on peripheral hormone levels (Wingfield et al. 1997; Adkins-Regan 2008). We have only a brief window of perspective on the cycle of extinction and adaptive radiation. The ability to include expansive, as well as reductionist perspectives may facilitate new thresholds in our evaluation of environmental, social, behavioral and clinical aspects of sex-steroid biology.

8. Abbreviations

ancSR = Ancestral Steroid Hormone Receptor; AR = Androgen Receptor; CG = Chorionic Gonadotropin; ER = Estrogen Receptor; FSH = Follicle Stimulating Hormone; GR = Glucocorticoid Receptor; hCG = Human Chorionic Gonadotropin; HPA = Hypothalamic-Pituitary-Adrenal; HPG = Hypothalamic-Pituitary-Gonad; HPT = Hypothalamic-Pituitary-Thyroid; insl3 = Insulin-like hormone 3; LH = Lutenizing Hormone; MR = Mineralocorticoid Receptor; SHBG = Steroid Hormone Binding Globulin; TSH = Thyroid Stimulating Hormone;

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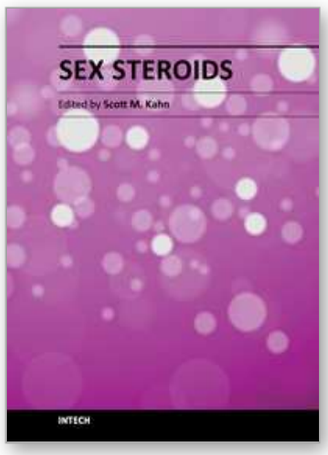

Sex Steroids

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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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