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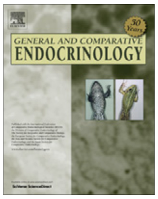

Review

Hormonal organization and activation: Evolutionary implications and questions

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ABSTRACT

Comparative endocrinology is a fascinating field of science in part because it addresses both ultimate and proximate causation. Research on sexual dimorphism and sexual differentiation has excellent potential for this kind of integration. Vertebrate comparative endocrinologists have made many important discoveries about the role of genes and sex steroid hormones in the organization and activation of sexually differentiated behavior, brain function, anatomy and physiology. In addition to taxonomically general principles and conserved features, there is also striking diversity in sexual differentiation processes. Much of the evolutionary basis of this diversity (its phylogenetic history and adaptive functions) is not well understood. A set of questions is raised to illustrate this point, with an emphasis on mechanisms of sexual dimorphism in body size and ornamentation, sexual differentiation of avian behavior, particularly in Japanese quail and zebra finches, and the puzzle of the phylogenetic distribution of vertebrate sex determining mechanisms. Applying a comparative approach grounded in established phylogenies and concepts from evolutionary developmental biology such as developmental modules holds promise for generating and testing new hypotheses and eventually answering some of these questions.

1. Introduction: asking evolutionary questions about endocrine mechanisms

Biology comes in two flavors. One flavor tackles questions about the internal machinery of life such as physiological and molecular mechanisms. The other addresses questions about ecology and evolution, including the history of life as well as processes resulting in change and adaptation to environments. The scientific goals of these two flavors are often referred to as proximate and ultimate causation [46]. The two sets of questions are known as "how" and "why" questions. Comparative endocrinology is a fascinating field of science in part because it can integrate both flavors. It can contribute to an understanding of evolution by illuminating the mechanistic biases for trajectories over time. It puts endocrine mechanisms in an evolutionary context to ask about their history over time, the ecological and other selective pressures and processes that have produced them, and the ways in which they are adaptive (aid fitness) (see, for example, the extensive comparative analysis of Hahn et al. [32] aimed at understanding evolutionary changes in the regulation of the gonadotropin-releasing hormone system related to flexible breeding in birds). These are compelling questions both for conserved features of endocrinology (those that are old, widely shared, and characteristic of a major branch of the tree of animal life, such as the role of thyroid hormones in chordate metamorphosis [54]) and for more diverse and taxon specific features (such as the androgen 11-ketotestosterone that is found only in teleost fish). "Why" questions can be asked at both a microevolutionary scale, as in Williams' [72] focus on individual variation in hormone based traits (the raw material for evolutionary change), and at a macroevolutionary scale, as in this review. Many of these intellectually compelling evolutionary questions are still unanswered, or the conventional answers are not very satisfactory because they are not sufficiently well informed by modern evolutionary thinking. The bright side of this situation is the tremendous opportunity for young investigators to make major contributions.

The comparative endocrinology of reproduction, like reproductive biology generally, is an especially rich source of inspiration for asking "why" questions about mechanisms. Living animals possess an impressively diverse array of elaborate and even bizarre devices and products for achieving reproduction that reflect the operation of sexual selection (mate choice and mate competition) along with other forms of natural selection. A prime example that has received much recent attention is sperm, which come in an astounding variety of shapes and sizes (including sperm that are many times longer than the males themselves) that are known or hypothesized to result from sexual selection [12].

Even basic reproductive anatomy raises a number of "why" questions, including old classics of the field that have not yet been answered. Why are the testes of many mammals located outside the body cavity (descended into a scrotum)? Why are mammals

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the only animals on earth that ever locate them there? The old textbook answer, that sperm cannot be produced at the body's internal temperature, makes no sense to anyone who studies birds, who have hotter bodies than mammals (40 °C for birds vs. 36–38 °C for mammals according to Calder [16]), yet never have external testes. A number of other hypotheses have appeared in the literature. For example, it was proposed by Portmann back in 1952 [58] that external testes served a signaling function. While this might seem like an odd idea, it is certainly the case that a location outside the body cavity is a very risky place for something so critical for evolutionary fitness, especially for animals that have teeth and claws. Anyone familiar with Zahavi's handicap theory of signal honesty will immediately recognize that risk or other costs are key to the evolution of extravagant sexually selected signals [77]. Neither this nor any other hypotheses for the evolution of mammalian testis location have received a proper test, however. With respect to evolutionary history, recent mammalian phylogenies allow an estimation of the mammalian ancestral testis location (internal, as in other vertebrates), how many times externalization of the testes has evolved (once or twice), and when those origins of a new location occurred (about 150 and 100 million years ago) [39]. We can expect progress in the future identifying other new traits or ways of living that arose at about the same time that might provide clues to the function of the changed testis location.

Continuing with gonads, we can ask why the testes of vertebrate males produce masculinizing hormones as well as gametes, whereas the masculinizing hormones of crustaceans are produced by a separate non-testicular gland, the androgenic gland [63]. One of the interesting consequences of this crustacean separation of functions is sex reversal of amphipods and isopods by parasitic "castration," in which infection with parasites destroys the androgenic gland and the genetic male host becomes a functional egg producing female [62].

On the female side, another old classic question is why female birds usually have only one functional ovary. It is usually hypothesized that this has something to do with flight. Once again, progress answering this question is likely to come in part through "tree thinking," that is, by placing the phenomenon on a phylogenetic tree that includes fossil ancestors [67]. Such trees of fossil birds and non-avian dinosaurs have led to new insights into the initial origins and functions of feathers. Similarly, we can look forward to a test of the hypothesis that the origin of one-sided egg production coincided with the origin of flight.

Moving closer to questions about vertebrate hormonal organization and activation, a number of researchers have asked why sex change (functional adult sex reversal as an adaptive part of reproductive life history) has evolved repeatedly in some teleost fish clades but is absent in other vertebrates. Does the difference lie in ultimate causes (it benefits teleost fish more than it would benefit other vertebrates)? To what extent is the likelihood of such an evolutionary trajectory facilitated by something special about the gonadal sex determination of teleosts? The idea that proximate mechanisms might bias the odds toward ending up at one particular phenotypic state ("adaptive peak") rather than another when selection pressures change draws on the concepts of adaptive landscapes and of mechanisms as potential constraints or facilitators of evolutionary change [57]. Alternatively, we can ask whether the existence of sex-changing teleosts is a simple statistical and historical consequence of the fact that there are a lot more teleosts than other vertebrates, making rare origins more numerous. Less common are questions about why testosterone is the steroid molecule that males use for making sperm and some other masculine functions, whereas estradiol is the female analog [76]. What would not work as well if it were the other way around? If testosterone is so good for maleness, why do so many vertebrates turn it into estrogens in the brain in order to express masculine behavior? Why do teleost fish in particular have such high levels of brain aromatase (the enzyme that converts androgens to estrogens) [17]?

2. Sexual differentiation

Animals that come in two sexes undergo a process of sexual differentiation. "Sexual differentiation" refers to the developmental pathways resulting in sex differences in anatomy, physiology, nervous systems, and behavior. Understanding sexual differentiation has long been an important part of comparative endocrinology, and in the case of some animal groups it is one of its many success stories. As is now well known, two key categories of mechanisms are sex genes and gonadal sex steroid hormones. Research in recent years has shown that much (but not all) of the molecular cascade downstream of the sex genes that is responsible for ovary vs. testis development is remarkably conserved among vertebrate clades [44,45,75]. Another conclusion is the important role of the aromatase and estrogen receptor genes in the early stages of the ovarian sexual differentiation process [41,48]. These estrogenic mechanisms are produced early, before the gonads have differentiated. Gonads of teleost fishes, reptiles, and birds are readily sex reversed by experimental manipulations that target these estrogenic mechanisms, with estradiol treatment producing functional ovaries in genetic males, and treatment with an aromatase inhibitor producing functional testes in genetic females (see Fig. 1 for an example from the avian world). Yet such treatments don't have these dramatic effects in mammals. Instead, the estrogenic mechanisms appear later in gonadal differentiation, and seem to be a result, rather than a cause, of ovarian differentiation [24]. Why do these estrogenic mechanisms play a lesser role in mammalian gonadal differentiation? It cannot just be because mammals are viviparous and the mother's estrogens would harm testicular differentiation, because viviparity with maternal provisioning of embryos has evolved many times in other vertebrates [60].

What is reasonably well understood in mammalian sexual differentiation is the important role of gonadal sex steroids in organizing and/or activating other sex differences, including external reproductive anatomy, physiology, nervous systems, and behavior. The basic concepts of hormonal organization and activation of behavior originated with a classic paper by Phoenix et al. [55]. In contemporary terms, activation refers to increased expression at puberty or in adulthood, as when hormones stimulate growth of

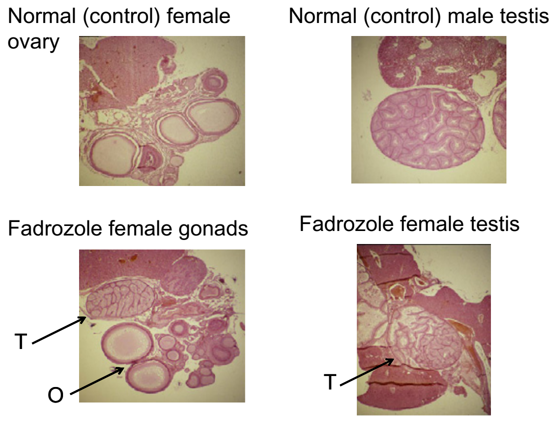

Fig. 1. A single injection of an aromatase inhibitor (fadrozole) on day 5 of incubation results in partial or complete masculinization of genetic female zebra finch (*Taeniopygia guttata*) gonads, indicating an important role for estrogenic mechanisms in sexual differentiation of the gonads [5]. The adult female on the bottom left has a testis (T) and an ovary (O); the one on the bottom right has a testis and no ovary.