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Review

Prenatal environmental influences on the production of sex-specific traits in mammals

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ABSTRACT

The determination of offspring sex represents a delicate balancing act during which offspring must pass through several developmental levels in the presence of influential environmental factors. Successful expression of sex-specific traits requires genetic and hormone-based effects on several organizational and activational levels. Environmental factors can exert controls and disruptions at each of these levels. This review addresses the developmental stages at which environmental factors may influence the processes of sex determination, with an in depth focus on the prenatal stages, including the production of the primary and secondary sex ratios and the differentiation of functional secondary sexual characters.

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1. Introduction

The successful production of an individual of a particular phenotypic and functional sex relies upon a series of steps and processes that extend throughout the individual's life. Development into a sexually functional and actively breeding individual requires genetic and hormone-based effects on several organizational and activational levels (Fig. 1). Part of this process lies within maternal and/or paternal control; sex allocation and fetal programming are well-documented ways in which parents can optimally match offspring phenotype to the birth environment, thereby maximizing fitness potential. After parturition, exposure of the offspring to environmental variables through puberty and adulthood can further shape how well the individual survives and functions reproductively. As a result, environmental variables and influences are potent determinants of reproductive success.

The initial establishment of whether an individual mammal will become male or female begins with gametogenesis within the adult male and ends at fertilization. At this point the primary sex ratio, the number of males versus females initially produced at the point of gamete fusion, is established. Following fertilization, the number of males and females produced, at this point termed the secondary

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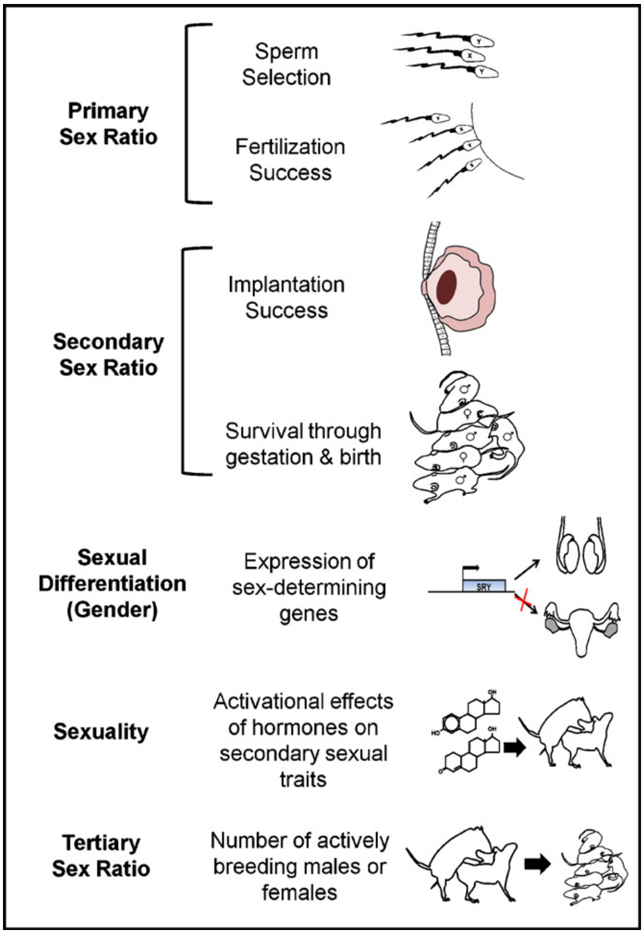

Fig. 1. The stages of sexual development during which environmental variables can significantly affect the reproductive outcome. The primary sex ratio, the initial determination of the genetic sex of offspring at fertilization, can be influenced by factors that alter the production, mobilization, and/or fertilizing capacity of X versus Y-bearing sperm. The secondary sex ratio, the ratio of males to females after fertilization, depends upon the survival of male versus female offspring from the blastocyst stage through adulthood. The phenotypic sex of offspring can be altered by environmental events that disrupt organizational processes of sexual differentiation *in utero*, and the tertiary sex ratio, or the number of individuals that actively breed depend upon activational events on physiology as well as social interactions during adulthood.

sex ratio, can only be altered through sex-specific embryonic, fetal, or natal loss (Fig. 1). Adaptive theory suggests that parents should produce an optimal offspring sex ratio based upon conditions into which offspring will be born. This is because each sex comes with its own set of fitness costs and benefits, and selectively thrives in environments where, for example, food is abundant, mates are numerous, or competition is fierce. Thus many environmental factors, including resource availability, the social environment, and seasonal cues may affect the ratio of male to female offspring produced.

Moving forward in the developmental timeline, environmental variables can also influence the translation of the sex chromosomes into a phenotypic sex. Processes of sexual differentiation are particularly vulnerable to slight hormonal and physiological perturbations, as the organization of many sexual characteristics are restricted to a critical period within development. Processes of sexual differentiation can be divided into two main stages: during the pre-gonadal stage, sex chromosomes are primarily responsible for determining whether the primordial germ cells differentiate into either male or female gonads. In mammals, the expression of testes determining genes found on the Y chromosome, such as SRY, is responsible for shifting the differentiation of the gonadal primordium towards testicular development. In the absence of testis determining genes, primordial germ cells develop into an ovary (reviewed in Ref. [1]). Thus, in mammals, the default sex is female. Changes mediated by the epigenetic environment of embryogenesis can permanently disrupt gonadal morphology and function.

The post-gonadal stage is characterized by the actions of hormones on the remaining portions of the reproductive tract as well as the organization of the brain and behavior [1]. In mammals, the fetal testes produce testosterone which masculinizes the remainder of the reproductive tract, stimulates formation of the male external genitalia [1], and causes masculine patterns of brain development that last into adulthood [2]. Environmental and hormonal perturbations that disrupt the normal testosterone peak during critical stages of fetal development can have long-term effects on physical and behavioral function throughout an individual's life.

Given individuals that have successfully developed and differentiated into phenotypic male and female individuals, there is also a potential for environmental factors to influence the sexuality of the individual, or the secondary sexual characters and behaviors exhibited during adulthood, in a sex-specific way. And finally, given a sexually capable individual, the ability for successful breeding is also challenged through social and environmental interactions, potentially altering the tertiary or operational sex ratio, which is the number of actively breeding males and females in a population (Fig. 1).

Each level of sex determination is subject to a variety of environmental variables that can either stimulate the production of one sex over another, or disrupt the process entirely, preventing individuals from eventually producing a successful breeding attempt. Bronson stated that the diverse environmental factors that can influence a mammal's reproductive performance can be classified as either dietary, physical, or social in origin [3]. When environmental effects are translated through maternal mediation, we can also discuss those influences in a more specific, mechanistic manner, examples of which include environmental influences on endogenous hormone concentrations during gametogenesis, intrauterine hormonal milieu during gestation, vaginal acidity at the time of insemination, and others. Here we focus on prenatal influences on mammalian sex determination. We review the many environmental factors that may influence the ratio of male to female offspring produced and the differentiation of those individuals into phenotypic males or females.

2. Food abundance

2.1. Primary and secondary sex ratio

A common thread among many adaptive theories concerning sex allocation is the idea that offspring sex ratios should vary with resource availability, and related maternal and/or paternal quality (reviewed in Ref. [4]). Indeed, skews in the mammalian sex ratio according to the quality and quantity of available food have been documented in many species. Female mice (*Mus musculus*) fed intermittently produced significantly fewer sons compared to females fed *ad libitum* [5] and female Syrian hamsters (*Mesocricetus auratus*) produced significantly less males when food was restricted throughout pregnancy and lactation [6]. Food restriction of female mice 1 week prior to mating resulted in significantly lower sex ratios (less males) compared to controls [7]. These effects extend beyond laboratory animals—dairy cows (*Bos taurus*) given a highly nutritious diet produced significantly more males compared to cows on a less nutritious diet [8], and heavier female mule deer produced significantly more male offspring [9]. Nutritional effects on offspring sex ratio even apply to humans; African women show-