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Review

Establishing Sexual Dimorphism in Humans

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A B S T R A C T

Sexual dimorphism, i.e. the distinct recognition of only two sexes per species, is the phenotypic expression of a multistage procedure at chromosomal, gonadal, hormonal and behavioral level. Chromosomal – genetic sexual dimorphism refers to the presence of two identical (XX) or two different (XY) gonosomes in females and males, respectively. This is due to the distinct content of the X and Y-chromosomes in both genes and regulatory sequences, SRY being the key regulator. Hormones (AMH, testosterone, Insl3) secreted by the foetal testis (gonadal sexual dimorphism), impede Müller duct development, masculinize Wolff duct derivatives and are involved in testicular descent (hormonal sexual dimorphism). Steroid hormone receptors detected in the nervous system, link androgens with behavioral sexual dimorphism. Furthermore, sex chromosome genes directly affect brain sexual dimorphism and this may precede gonadal differentiation.

Key words: *SRY, Insl3, testis differentiation, gonads, androgens, AMH, Müller / Wolff ducts, aromatase, brain, behavioral sex*

Introduction

Sex is a set model of anatomy and behavior, characterized by the ability to contribute to the process of reproduction. Although the latter is possible in the absence of sex or in its multiple presences, the most typical pattern and the one corresponding to humans is that of sexual dimorphism. The term sexual dimorphism has been used to describe morphological differences between the sexes, but can be extended to any biologically-related process that varies between males and females[1].

This quality achieves to offer the necessary variability in phenotype features, in gametogenesis and parental chromosome fusion in fertilization, while at the same time it ensures the maintenance of androgens and estrogens within an acceptable proportional ratio. Thus, sexual dimorphism is the phenotypic expression of a multistage procedure at chromosomal, gonadal, hormonal and behavioral level.

Chromosomal – Genetic Sexual Dimorphism

In humans, the typical male usually has a diploid karyotype of 46 chromosomes, including 22 autosomal pairs and an XY pair of gonosomes (46, XY). Alternatively, a standard female karyotype would be 46, XX, the latter referring to the two identical gonosomes in each diploid cell.

The basis of sexual dimorphism in mammals derives from the evolution of the sex chromosomes[2]. According to recent findings, both X and Y chromosomes have evolved from autosomal ancestors about 300 million years ago[3,4]. At the time, a failure in homologous recombination resulted in the formation of a small area that wasn't identical in the two chromosomes. The presence or absence of this region coincided with a different pattern of development that altered androgen activity, resulting in a sex – determining role. In all mammalian organisms surviving today, this area appears to retain the regulatory function and is therefore described as the sex-determining region of the Y chromosome (*SRY* gene)[5]. However, it must be pointed out, that the genetic basis of sexual dimorphism is not limited to a single gene. In fact, sequence analysis has suggested a gradual structural conversion process. According to this theory, the X and Y chromosomes have experienced repetitive recombination failures throughout time, leading to the accumulation of micro- and macroscopic specializations, which finally lead to the extensive differentiation in the current structure of the two gonosomes[4,6–8].

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The particularly small Y chromosome, in comparison to its X partner, cannot be simply attributed to chromosomal recombination. Therefore, one must assume that every failed recombination was followed by some level of genomic instability, which caused partial deletions of the Y chromosome-ancestor. Today, males carry a Y chromosome that almost entirely (95%) consists of non-recombinant sequences, allowing recombination with the X chromosome only in polar regions, the so-called pseudoautosomal regions, PAR1 and PAR2[9]. The non-recombinant region (NRY) seems to have developed around the *SRY* gene to include a variety of genes and regulatory elements that cooperate to produce the main features of the male phenotype. Owing to this observation, it has recently been proposed to rename this area as the male-specific region of the Y chromosome, or MSY. Moreover, it has been suggested that the MSY has the ability to exchange DNA between its own different units, allowing some level of variability. This unique quality is based on the presence of palindromes, which increase its stability and determine the positions of Y-Y recombination[9–12]. According to this, one should expect that, the Y chromosome retains its current length, after millions of years of gradual deterioration, a concept that remains to be proven[9,13,14].

For females, the double presence of the X chromosome seems to be related to sexual features. However, in all higher mammals that have developed an MSY region, extending the sex determining abilities of the *SRY* gene, some model of X chromosome inactivation has been employed[15]. This mechanism leads to dosage compensation between the two sexes for the large majority of X-linked genes[6]. The remaining genes escape inactivation, which predisposes for their differentiated role in females, owing to their double expression from the two X chromosomes, as opposed to a single copy in XY males. However, not all of these genes have been found to control sex-related functions. Therefore, one may assume that certain autosomal genes must also play an important role in the establishment of the female sex pattern.

The crucial role of the sex chromosomes in dimorphism is particularly stressed by the phenotypic disorders associated with cytogenetic alterations. Despite differences in their clinical manifestations, gonosome aneuploidies, such as Kleinefelter and Turner syndromes, are always characterized by gonadal dysgenesis and infertility.

Gonadal Sexual Dimorphism

The expression of the *SRY* gene is the key parameter in gonadal differentiation. In males, *SRY* is expressed in differentiating epithelial cells of the gonadal anlagen, i.e. Sertoli cells that encompass germ cells forming the seminiferous cords[16,17]. *SRY* is expressed only briefly, and therefore, one may assume that it acts as a form of molecular "switch", triggering a gene cascade that promotes male phenotype (Table 1, Figure 1). Indeed, of the numerous downstream genes, current research mainly focuses on two major gene products, both deriving from Sertoli cells. The first is the SOX9 protein, which appears to coordinate the formation of seminiferous cords within the developing testis. The action of SOX is necessary for

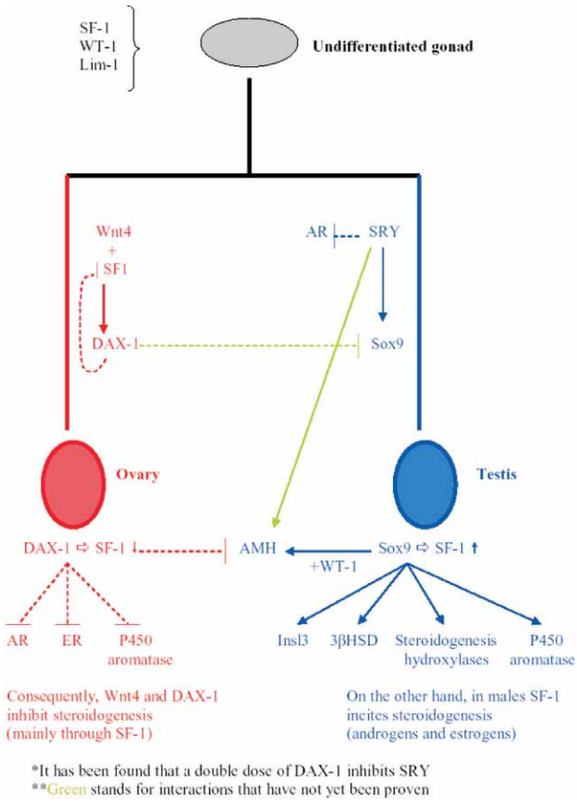

Fig. 1. Genes implicated in gonadal sex differentiation.

TABLE 1
MOLECULAR MARKERS IN THE EARLY STAGES OF GONADAL DIFFERENTIATION IN THE RAT FOETUS

Molecular markers	Testis (XY)	Ovary (XX)	Molecular markers	Testis (XY)	Ovary (XX)
11.5 days *post conception* (*dpc*)			12.5 days *post conception* (*dpc*)		
Sry	+	–	*Sry*	–	–
SOX9	++	–	*SOX9*	++	–
DAX1	++	++	*DAX1*	+/–	++
AMH	–	–	*AMH*	++	–

normal testis development, since its absence totally inhibits it, regardless of *SRY* expression, as experiments with mutant SOX deficient mice have shown. This involves both Sertoli and Leydig cells, since the latter are induced by SOX9 to express the *FtzF1* gene, whose product is the main regulator of androgen production, i.e. steroidogenic factor 1 (SF1)[18,19].

Although testis formation is largely androgen-independent, it seems that subsequent development of the organ depends on continuous trophic exposure to androgens. The latter are produced by Leydig cells and accumulated by the androgen binding protein produced by Sertoli cells. Experimental data in adult rats show that a stable androgen to estrogen ratio is vital to retain both ovary and testis histological organization.

Testosterone promotes Wolffian duct differentiation into the male reproductive tract through the formation of the epididymides, vas deferentia and seminal vesicles. On the other hand, Sertoli cells produce the Anti Müllerian Hormone (AMH), shortly following *SRY* stimulation. This hormone inhibits the development of the Müllerian ducts in the male embryo[20–22].

In females, absence of the *SRY* gene allows the formation of an ovary. Among the major regulators of this process, one may refer to the DAX1 protein, which is associated with follicular cell function and the formation of the primordial follicles. The importance of this product is understood by the result of its duplication in male rats. In this case, regardless of *SRY* or *SOX* action, DSS-AHC critical region on the X chromosome gene 1 (*DAX1*, also known as *NrOb1*) achieves the feminization of the genital structures, a process described as dosage-sensitive sex reversal[23]. In addition, experimental data suggest that its presence, in small quantities, in males, may actually be required for the initial organization of the epithelium forming seminiferous cords. As far as ovaries are concerned, steroid producing cells are represented by the inner and outer theca. The SF1 protein is the key regulator of androgen production in these cells as well, but it also helps to limit P450 aromatase activity, thus achieving an optimal androgen to estrogen ratio.

In the absence of male hormones, the Wolffian ducts degenerate, whereas the Müllerian ducts persist and differentiate into the female reproductive tract, including the oviduct (fallopian tube), uterus, cervix and upper portion of the vagina. Homeobox A (*Hoxa*) genes are expressed along the craniocaudal axis of the Müllerian ducts and specify the identities of the developing structures. The expression of a *lin-11*, *Isl1* and *mec-3* homologue (*Lim1*, also known as *Lhx1*) which encodes a LIM class homeodomain protein, in the epithelium of the Wolffian and Müllerian ducts highlights the initial sexual duality of the forming reproductive systems[24,25].

Hormonal Sexual Dimorphism

The external genitalia and the secondary sex features, such as osteology, muscular strength, voice depth, hair length, lipid distribution pattern, facial characteristics and breast development, are controlled by androgens and estrogens[26–29]. Both types of hormones may act in androgen and estrogen receptors, thus altering the outcome at a cellular and tissue level. It is important to note that, while estrogens mainly act in the form of estradiol, i.e. the final product in the aromatase chain of reactions, androgens act as both, testosterone, and the most enhanced form, dihydrotestosterone (DHT). The latter is produced from testosterone by the action of the enzyme 5a-reductase. Testosterone and DHT bind to a specific high-affinity intracellular receptor and, ultimately, this hormone-receptor complex enters the nucleus and modulates transcription of tissue-specific genes and their protein products. Testosterone-receptor complex mediates development of the Wolffian derivatives whereas DHT-receptor complex modulates differentiation of the urogenital sinus and male external genitalia. The response of target tissues to testicular hormones lasts for a particular developmental period, which constitutes the sensitive period for hormone action. Hormonal treatment of females in adulthood has negligible effects on genital morphology[27]. The differentiation of external genitalia into labia majora, labia minora, clitoris and part of the vagina is stimulated by estrogens. Androgens together with AMH and insulin-like growth factor 3 (Insl3) are involved in testicular descent to the scrotum, via activation of the Lim1 transcriptional factor. In the female embryo, the absence of androgen holds the ovary by the suspensory ligament inside the abdomen and, as Insl3 is not present, the gubernaculums fades away before it has a chance to yank the ovary outside[30].

Sexual Dimorphism of the Brain

Until recently, scientists believed that the way in which each individual chooses to determine his/her sex constitutes a final, "behavioral" level in sexual dimorphism, attributed to psychological rather than organic factors. However, it has been suggested that sex hormones might be involved in processes within the central nervous system (CNS) which cannot explain sexual preferences, but they may constitute some kind of predisposition to homo- or hetero-sexuality. This concept has given rise to extensive research on this field of Neuroscience, leading to reviews and original papers on the issue of the so-called "sexual brain"[31,32].

Of the various functional regions of the CNS, those that seem to be closely associated with the sexual behavior are the hypothalamus, the amygdala and the bulbocavernosus nucleus in the spinal cord. The hypothalamus represents a central area in the regulation of the autonomous nervous system and the function of vital organs. Regions related to sexual dimorphism, perinatally, include the preoptic area and the anteroventral periventricular nucleus, both bearing estrogen receptors. On the other hand, the septal AVP, the spinal bulbocavernosus nucleus (SBN) and the nucleus robustus archistriatum seem to retain a role in sexual differentiation throughout life. With the exception of the SBN, which

only contains androgen receptors, the others seem to be regulated by both androgen and estrogen receptors (glutamate secreting neurons). This is true for the posterodorsal medial amygdala in adults. Progesterone, on the other hand, is known to bind to the subunit of GABAnergic neurons.

Although the exact target for sex hormone activity in the CNS is not clear, research has provided some probable candidates. These include, for example, the ciliary neurotrophic factor (CNTF) receptor, which regulates neuronal development. Moreover, PGE_2 may promote "masculinization" of the preoptic area in the hypothalamus, but it cannot justify the differences in volume observed between the two sexes. Granulin is an androgen-induced modulator of epithelial growth, highly expressed in the ventromedial and arcuate nucleus of the hypothalamus[33]. Prenatal exposure to high androgen concentrations is often found in the history of homosexual women, while androgen insensitivity is detected in some men submitted to surgical sex reversal.

Differences between male and female brains are thought to arise largely through the actions of gonadal secretions during a critical period of brain development[34]. In humans (as in rats) circulating testosterone displays 2 peaks. The 1st peak, in male human embryo, occurs in the 2nd trimester of gestation and the 2nd peak in the 1st year of post-natal life (Figure 2). Thus, higher levels of testosterone during foetal and neonatal life cause the masculinization of the brain[31,32].

Due to the fact that, specific central nervous system regions and behavior can be fully sex-reversed by treating females with testosterone or preventing the action of testicular hormones in males, no other factor need to be invoked in order to explain the sexual differentiation process in those cases[35].

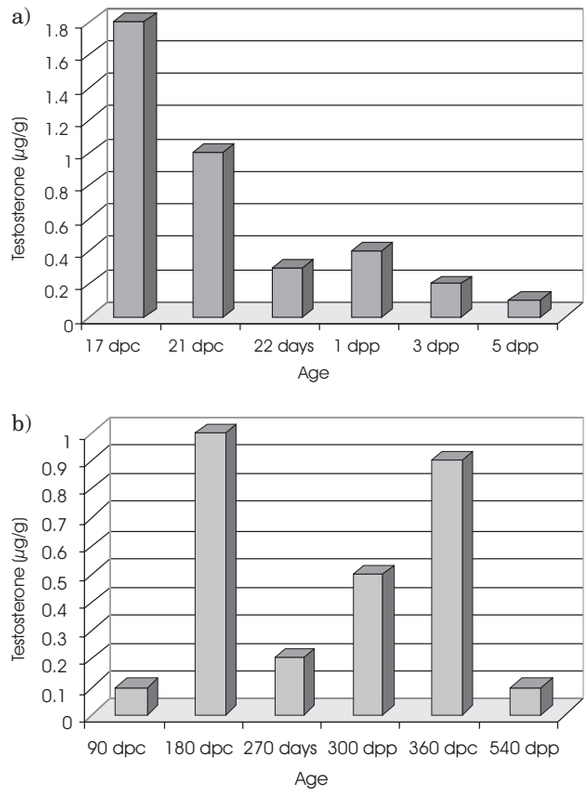

Fig. 2. Levels of testosterone in foetal and neonatal a) rats and b) humans: dpc – days post conception, dpp – days post partum.

Testis-Dependent Sexual Dimorphism

Several masculinizing effects of androgens in the brain result from aromatization of testosterone to estrogen, catalyzed by aromatase, an enzyme abundant in the hypothalamus[36]. Only aromatizable androgens, such as testosterone, exert a masculinizing effect in female rats, not non-aromatizable androgens, such as 5µ-dihydrotestosterone (5µ-DHT). But, in addition to aromatase, the brain contains 5µ-reductase. The type 2 isoform of 5µ-reductase (5µ-R2) is expressed in cerebral neurons and its maximal expression occurs a few days after birth, in males than in females. This enzyme (5µ-DHT) seems to be a morphogenetic signal for the development of aromatase-expressing neurons of the hypothalamus[32]. However, the importance of 5µ-DHT in brain masculinization is limited because men with homozygous inactivation of the 5µ-R2 gene and their animal model (5µ-R2 knock-out mice) display a proper gender identity and behavior[37,38].

Lesions of the entire preoptic area (POA) in the anterior hypothalamus eliminate virtually all male copulatory behaviors, whereas lesions restricted to the sexually dimorphic nucleus of the POA (SDN-POA) have more modest effects. Treating female rats with testosterone, just before and after birth, causes the SDN-POA in adulthood to be as large as in normal males, whereas castrating male rats at birth results in a smaller feminine SDN-POA in adulthood. Thus, sexual differentiation of this nucleus resembles that of the genitalia, i.e. androgen early in life permanently masculinize this brain region[39–41].

However, a divergence has been observed on these neural sexual dimorphisms. Some rely on perinatal actions of testosterone (SDN-POA, AVPV) and some require both perinatal and adult testosterone (septal vasopressin, BNST, SNB, RA)[34]. Yet, others require testosterone only in adulthood (MePD – Prostero Dorsal Medial Amygdala)[41, 42]. In some cases, testosterone acts only on estrogen receptors (SDN-POA, AVPV) or activates both androgen and estrogen receptors (septal vasopressin, MePD, RA)[43, 44]. In other cases, only androgen receptors act perinatally (SNB).

Testis-Independent Sexual Dimorphism

Recent studies have shown that, sex-specific differences observed in both mammals and birds can be associ-

ated with X and Y chromosome-linked genes acting directly on the brain cells[45]. In several species of songbirds, males sing more than females, a functional difference that matches a structural difference: the forebrain regions controlling song, including the Higher Vocal Center (HVC) and the nucleus Robustus Archistriatum (RA). These nuclei are much larger in males and contain larger neurons, than their female counterparts. The forebrain song circuit shows marked sexual differentiation, which does not seem to be due solely to gonadal hormones, but rather might result from differences in neuronal sex chromosome genotype[46].

Manipulating males with gonadal estrogen do not prevent masculine development, so it seems that brain cells may produce *de novo* estrogen (neurosteroids) to induce HVC ingrowth and masculine development. Neuronal transplantation studies in quails also support a role for genetic sex in controlling sexual differentiation in the brain. This means that, an important contribution to the process of brain sexual dimorphism is given by the action of sex chromosome genes, acting locally, within the brain (somatic) cells and steroid hormones are produced *in situ*, to virilize the bird song system[47].

Microarray screening of genes that were expressed differentially in the brain of male and female mice, before gonadal hormone secretion, allowed the identification of 57 female enhanced genes and 24 male enhanced genes, at embryonic day 10.5 (E10.5). This means that sexual differences in gene expression in neuronal cells, before gonadal hormone secretion, play an important role in sexual dimorphism in the brain[48,49].

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SPOLNI DIMORFIZMA KOD LJUDI

S A Ž E T A K

Spolni dimorfizam, odnosno raspoznavanje dvaju spolova unutar vrste, fenotipska je ekspresija višefaznog postupka na kromosomskoj, gonadnoj, hormonalnoj i bihevioralnoj razini. Kromosomsko-genetski spolni dimorfizam odnosi se na postojanje dvaju identičnih (XX) ili dvaju različitih (XY) gonosoma kod žena i muškaraca. To je posljedica različitog sadržaja X i Y kromosoma na oba gena te regulatorskih sekvenci, a SRY je ključni regulator. Hormoni (AMH, testosteron, Insl3) koje izlučuju fetalni testisi (gonadni spolni dimorfizam) priječe razvoj Müllerovog duktusa, maskuliniziraju derivate Wolffovog duktusa te su uključeni u testikularno propadanje (hormonalni spolni dimorfizam). Receptori steroidnih hormona, nađeni u živčanom sustavu, vežu androgene uz bihevioralni spolni dimorfizam. Nadalje, geni na spolnim kromosomima direktno utječu na moždani bihevioralni dimorfizam, što može prethoditi gonadnoj diferencijaciji.