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The Role of Hormones in Sexual Differentiation in Man

Rola hormonów w różnicowaniu płciowym u człowieka

Abstract: The article presents fundamental information on the role of gonadal hormones in the developement of anatomical sex phenotypes and (via their effects on the brain differentiation) on the formation of gender identity and sexual orientation., The principal roles in these processes are played by androgen (mostly testosterone) in the fetal and peri-natal period in the male sex or their absence in the female sex. It is hypothesized that among the factors which can disturb these processes are environemental pollutants, which can interact with hormone receptors, including the receptors of sex hormones (s.c.endocrine disruptors, endocrine disrupting chemicals). The higher secretion of testosterone in men since the puberty leads to a stronger developement of muscles and skeleton, whereas the higher secretion of estrogens in women to the earlier end of a growing up process. It results in the inequality of physical strenght between women and men which had a significant influence on the formation of typical social roles of both genders, especially in the prehistorical period.

Introduction

Nowadays the questions linked with the formation of gender in man, especially of its psychoneurological aspects, becomes a field of a sharp public discussion. Sometimes this discussion becomes very aggressive and lacks the knowledge on the fundamental biological processes involved in this process. The article below presents fundamemntal data (often unappreciated) on the roles of gonadal hormones, androgens and estrogens in the processes of the

formation of gender identity and sexual orientation and also their indirect effect on the social position of both genders.

Chromosomal determination of the human sex

The feconded ovum (zygote) posseses 46 chromosomes. A half (23) of them are of maternal origin and the other 23 of paternal origin, furnished by spermatozoon. X and Y chromosomes are responsible for the determination of sex. To initiate the female sex the presence of two X chromosomes is necessary and the occurrence of X and Y chromosomes is obligatory for masculine sex. The presence of only one X chromosome with the absence of the second sex chromosome (X0, so-called Turner's syndrome) unables the developent of the gonads, but the female phenotype is preserved. In turn, the kariotype with sole Y chromosome (Y0) was never observed; it means that at least one chromosome X is necessary for life. With the presence of at least one Y chromosome, despite the presence of multiple X chromosomes (for instance, XXY s.c. Klinefelter's syndrome), the gonade develops as testis (although with some malformations) and the phenotype remains male.

Fetal differentiation of genital organs

Whereas in the female subjects the fetal ovary remains silent, the male gonade – testis is hormonally active. It secrets androgens (including the most acive of them, testosterone) and so-called antimullerian hormone (AMH). Testosterone and other androgens secreted by the male fetal gonades stimulate the developement of male internal and external genital organs. In turn, AMH evokes the atrophy of internal genital female pathways. In the absence of testis, and, in consequence, the absence of androgens, the primordia of masculine genital organs in the female fetus undergoes atrophy (see: Figure 1).

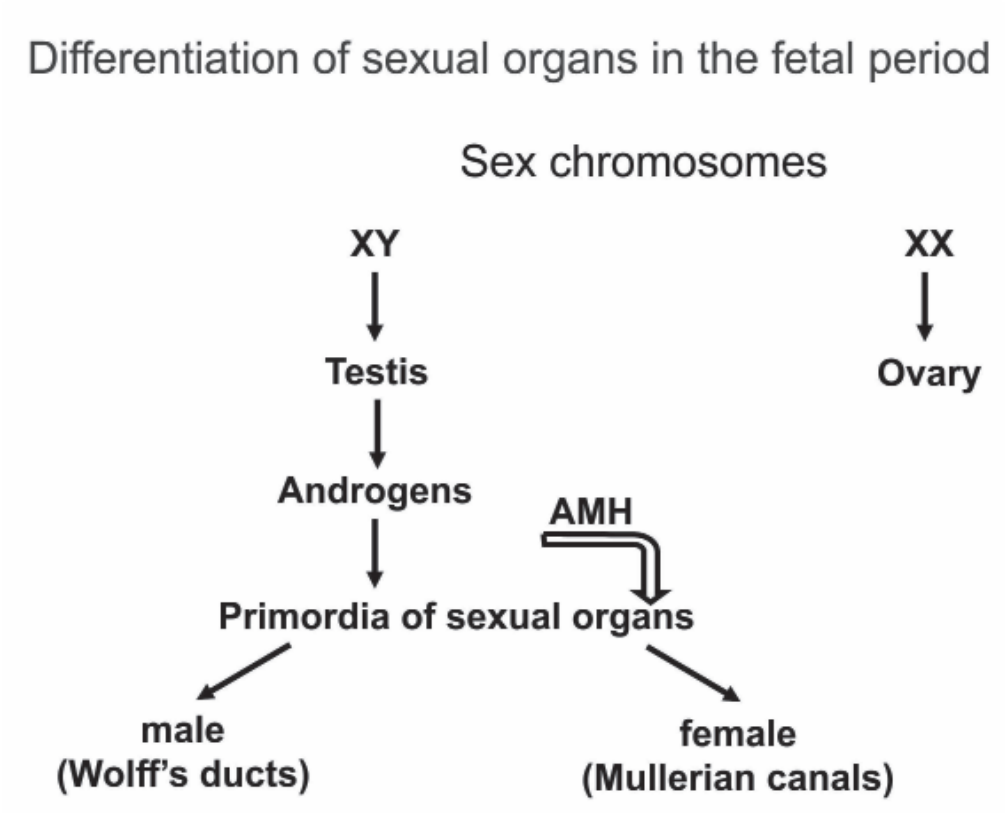

Figure 1.Differentiation of sexual organs in the fetal period
AMH – antimullerian hormone. Detailed explanation in the text

Peri-natal differentiation of the brain by sex hormonal interventions

The experimental studies on animals (mostly rodents) have shown that hormonal interventions in the critical peri-natal period induce irreversible changes in sexual behaviour. The castration of male newborns induces female sexual behaviour, whereas, the administration of testosterone to female newborns induces, in turn, male sexual behaviour (Phoenix et al., 1959; Pfaff and Sigmond, 1971). Let us remember, that the function of gonads in mammals, including man, is controlled by the so-called hypothalamo-pituitary-gonadal axis. This axis is represented as a neuro-hormonal cascade composed by a hypothalamic neurohormone gonadoliberin (gonadotropin releasing hormone, Gn-RH), two pituitary gonadotropins – follicle stimulating hormone (FSH) and luteinizing hormone (LH) and gonadal hormones, mostly estradiol and progesterone in females and testosterone in males (see: Figure 2). In this axis a feedback mechanisms operate: the increase of gonadal hormone levels induces the retrograde supression of gonadotropin

secretion The above negative feedback mechanism is present in both sexes. However, in the female sex another feedback also occurs, a positive one: a great level of estrogens evokes a sharp increase of gonadotropin secretion (mostly LH), which is necessary for ovulation. The above described positive feedbcka between ertrogens and gonadotropin secretion was found to be disturbed by testosterone administration during the critical peri-natal period.

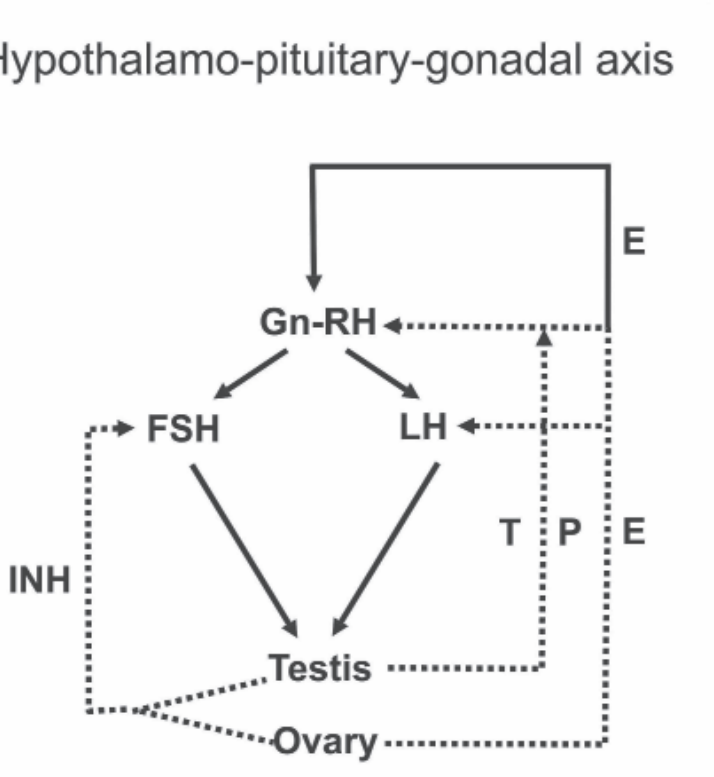

Figure 2. Hypothalamo-pituitary-gonadal axis. GnRH – gonadotropin releasing hormone

FSH – follicle stimulating hormone (folitropin); LH – luteinizing hormone (lutropin); T-testosteron; P- progesterone; E – estradiol; INH- inhibins (gonadal factors suppressing pituitary gonadtropins.Solid lines- stimulatory pathways; broken lines: inhibitory pathways

The limited period of age in which the above – mentioned procedures are effective and the irreversibility of their results suggest their deep influence on the anatomical and functional differentiation of the brain. Does similar mechanisms concern also the humans? Obviously, the results of experiments on animals cannot be simply transposed to man, but some observations in humans are compatible with above mentioned animal experimental data. Firstly, it was found that testosterone levels are markedly elevated in boys in comparison to girls in the early post-natal period.

(Forest et al., 1973; Forest, 1975; Hines et al., 2015). This period of enhanced testosterone levels in boys seems to be a critical period of sexual brain differentiation. Later, the levels of this hormone do not differ between boys and girls till the puberty. As it was mentioned above, in both genders a negative feedback between gonadal hormones and pituitary gonadotropins is present. It means that the elevation of gonadal hormones suppresses the gonadotropin secretion. However, in female sex we can observe a positive feedback – the increased secretion of gonadotropins (mostly LH) under the influence of the high concentration of estrogens. Several observations indicate disturbances of the positive feedback mechanisms in transsexual subjects (Seylar et al., 1978; Dorner et al., 1983; Kula et al., 1986). Summing up, these studies revealed the decreased evocability of pituitasry LH by estrogens and GnRH in women with female-to male transsexualism and increased evocabilty of LH under the influence of the same factors in men with male-to female transsexualism. The next important observations come from a „natural experiment" - a rare genetic syndrome called „complete androgene insensitivity" (CAIS) known also under the names of Morris' or Goldberg-Maxwell syndrome (Kucharska et al, 2018). CAIS is evoked by the mutations of the androgen receptor gene,leading to the total insensitivity to androgens, including testosterone (Pinsky et al., 1992). In these individuals, in spite of the male karyotype XY and male gonade (testis) secreting testosterone in abundance, the external phenotype, sexual identification and sexual orientation are female. Since testosterone cannot exert its proper action, it is transformed in a female hormone estradiol. At the time of puberty this situation leads to the developement of feminine shapes of the body (for instance, female breasts). For this reason the syndrome in question was also called the testicular feminization syndrome. Because the complete insensivity to androgens, which in both sexes is involved in the development of pubic and axillary hair at puberty, the individuals suffering from the CAI syndrome are described also as „hairless women". Similar observations come from another pathological syndrome, called the congenital adrenal hyperplasia (CAH). The pathogenesis of this syndrom is linked with the genetic defect of synthesis of the adrenocortical hormone, cortisol. The deficit of the cortisol production leads to the impairement of the retrograde inhibition of adrednocorticotropin (ACTH) secretion by pituitary, and ACTH overproduction causes the enhanced production of androgens by the adrenal cortex. This situation evokes numerous failures of female internal sex organs in girls, but also may disturb the formation of the gender identity and even sexual orientation. It was observed that

the girls affected by this syndrome frequently show in the childhood the preference to play in a way typical for boys, and, after the sexual maturity, they present the higher frequency of bisexual or homosexual orientation than it is observed in healthy women (Hines, 2008).

Summing up, the lesson from the observation of the above-described syndromes lead us to the following conclusion: the male phenotype as well the male sexual identity and typical heterosexual orientation are the consequence of the perinatal exposure to androgens (mostly to testosterone). Because the presence of androgens in the developement of masculine sex organs and the differentiation of the brain in the male direction are obligatory in the different time periods, it is possibile that the disturbance of these processes is separated. It means, that the undisturbed anatomical male or female phenotype can be accompanied by disturbed sexual identity. The presumption, that children are initially sexually undetermined, and develop further in the male or female direction only under the influence of the environement, although falsificated by the investigations on the hormonal brain differentiation (for review see: Kula and Słowikowska-Hilczer, 2000; Hines et al., 2015), nowadays remain still popular. The views on this question strongly depend on the spectrum of individual extra-scientific convinctions.

The possible dangers to fetal and/or peri-natal sexual differentiations in the modern world – Role of so- called endocrine disruptors

Nowadays we observe the increased frequency of disturbed sexual identity and orientation. Although this phenomenon seems to be unquestionably true, its dimensions are difficult to establish because of several psychological, social and even ideological and political factors influencing its manifestation. I would like to indicate the one hypothetical factor which might be one of the causes of the discussed phenomenon (usually not taken into consideration), namely the pollution of the environement. It is known that the great part of pollutants exert the interaction with hormonal receptors, mostly the receptors of steroid hormones. They are called endocrine disruptors or endocrine disrupting chemicals and have shown to affect brain developement and reproduction (Pinson et al., 2016).

Pubertal and post-pubertal effects of sexual hormones and their psychological and social consequences.

At the age of puberty, the activation of the hypothalamic-pituitary-gonadal axis takes place. The initiation of puberty is a complex process, regulated by many factors (see: Pawlikowski, 2000). The sexual hormones which

become to be secreted in abundance since the puberty evoke several important psychological and social consequences. Firstly, estrogens induce the changes in the body shape in girls, and their bodies become attractive to the majority of men. Secondly, the secretion of androgens, mostly of testosterone, results in a stronger developement of muscles and bones in men compared to women. Moreover, the higher secretion of estrogens in women results in a faster ossification of the epiphysial cartilages in women, and in the consequence the shorter medium stature in women. Both the factors result in the medium higher physical strength in men. In addition, a high level of androgens evokes higher aggressiveness in majority of men. In contrast, women in majority present higher empathy and develop maternal instinct, These factors had a deep influence on the social roles of both genders, establihed as early as in the human prehistory. The main role of men was to protect women and children against danger (role of warrior) and hunting, later, after the discovery of agriculture, also hard agricultural work. In turn, the role of women was the care of children and gathering. Athough this division of social roles between women and men seems to be optimal during the long period of prehistorical and historical existance of the mankind, it was - at least in part - responsible for the inequalitty of both genders in the society. The source of this phenomenon seems to be clear. On the top of a human tribe, nation or state a chief-warrior was situated. He was a warrior because of his great physical strenght and became a chief because of his great experince in combats. Although the source of such a situation is very distant in time, it persisted until our time. The lower position of women in a society resulted from a myth of lower intellectual ability of women in comparison to men. Although such a view is obviously false, some statistical differences are observed between female and male brains. The average weight of the masculine brain is greater (it correlates with the greater lean body mass) and posseses more abundant white substance (nerve fibers). Moreover, the longitudinal connections (situated in the same hemisphere) are prevalent. In turn, the average female brain contains more abundant grey matter (containing the nerve cells) and the tranverse (transhemispheral) connections are more abundant (Ingalhalikar et al., 2014). It is not known if these neuro-anatomical differences depend on the different hormonal profile. Moreover, several functional psychoneurologcial differences between women and men are described (for instance, higher empathy in women and higher aggressive behaviour in man). It should be underlined that the observed anatomical and functional dfferences are of statistical nature (it means that they concern the majority, but not every particular subject).

The very fast technological progress in our times results in the diminution of the importance of human physical force. In consequence, women set up the positions reserved till now mainly for men. It concerns even such positions, as leadership in administration and defence.

Conclusions

Hormonal mechanisms play a fundamental role in the formation of sex (gender) in man in anatomical aspect as well as (via differentiation of the brain) in the formnation of gender identity and sexual orientation. In the formation of genital organs during the fetal period, the principal role is played by androgens, mostly testosterone, or their absence. Similarly, the sexual differentiation of the brain, which takes place in the peri-natal period, depends on the presence or absence (or a low level) of androgens. Among the factors which can disturb this process the role of the environemental pollution is needed to be evaluated. Many „pollutants" can interact with hormone receptors, including the receptors of sex hormones (s.c. endocrine disruptors, endocrine disrupting chemicals). We cannot deny the significance of cultural and psychological factors but they play rather a secondary role in comparison with hormonal mechanisms. A further important moment of the influence of sex hormones is the period beginning with puberty. For instance, the higher secretion of testosterone in men leads to a stronger developement of muscles and skeleton, and the higher secretion of estrogens in women to the earlier end of growing up. It results in the inequality of physical strength between women and men which had a significant influence on the formation of typical social roles of both genders, especially in the prehistorical period.

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