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Testosterone and its metabolites – modulators of brain functions

Jaroslava Durdiakova[1, 2], Daniela Ostatnikova[2], and Peter Celec[1, 3, 4]*

[1]Institute of Molecular Biomedicine, Comenius University, Bratislava, Slovakia, *Email: petercelec@gmail.com; [2]Institute of Physiology, Comenius University, Bratislava, Slovakia; [3]Institute of Pathophysiology, Comenius University, Bratislava, Slovakia; [4] Department of Molecular Biology, Comenius University, Bratislava, Slovakia

Testosterone is a steroid sex hormone with an important role in the physiology in both sexes. It is involved in the development of morphological and functional parameters of the body *via* multiple molecular mechanisms. Intensive research focused on testosterone reveals associations with cognitive abilities and behavior and its causative role in sex differences in cognition. Testosterone modulates brain structure and the differentiation of neurons during intrauterine development with profound effects on brain functions during postnatal life. In this review we summarize the effects of testosterone on brain physiology and cognition with respect to the underlying molecular mechanisms.

Key words: testosterone, cognition, endocrine regulations, 2D/4D, sex differences

INTRODUCTION

Sex steroid hormones are mostly known for their role in the development of sex organs and physical maturation during puberty (Powers and Florini 1975, Kasperk et al. 1989, Toppari and Skakkebaek 1998, Bhasin 2000). Research on the effects of testosterone has brought many interesting findings that have radically changed and broaden the view of testosterone as a hormonal regulator of development. Animal experiments and human studies illustrate how testosterone influences putative unrelated features like morphological characteristics and cognitive abilities or intelligence (Martin et al. 2009, Hodosy et al. 2010). Our review summarizes the basic physiology of testosterone influencing not only morphological features but also cognition, emotions and behavior with respect to the underlying molecular mechanisms. The contribution of sex steroids to organizing structural and functional connections in the human brain is discussed, both during the prenatal period as well as during other period characterized by massive sex steroid changes such as puberty. The prenatal period is a critical time for sex steroids to shape the brain (Roy and Chatterjee 1995, Cohen-Bendahan et al. 2005, Manson 2008, Bull et al. 2010) but also for the development of the phalanges (Kempel et al. 2005, Malas et al. 2006). This is the reason why the length of the fourth digit (ring finger) is thought to be an index of prenatal testosterone exposure relative to the length of the second digit (index finger) the marker of prenatal estrogen level. According to several studies, 2D/4D ratio reflects hormonal background in uterus and is useful as a parameter to estimate early testosterone exposure (Manning et al. 1998, Manning and Taylor 2001, Rahman and Wilson 2003, Lippa 2006, Manning and Fink 2008). In this paper, a brief overview of studies investigating controversial relations between 2D/4D, prenatal testosterone exposure and various aspects of behavior and cognition is presented.

All behavioral traits, specific cognitive abilities of an individual are the result of a cooperation of hormonal, genetic and environmental factors. There are several known genetic variants modulating testosterone action and its final effect on target tissue (Greenland et al. 2004, Forstmeier et al. 2010, Haggarty et al. 2010). Several studies concerning genetic regulation of androgen activity are discussed in term of modulating final androgen activity.

Correspondence should be addressed to P. Celec, Email: petercelec@gmail.com

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Taken together, the goal of this review is to provide the comprehensive overview of testosterone physiology, cognition, social behavior and brain organization providing some issues for future research.

BASIC PHYSIOLOGY OF TESTOSTERONE

Testosterone is conserved through most vertebrates indicating its importance in evolution and development (Hau et al. 2000, Cornil et al. 2011, Sharma and Chaturvedi 2011). Testosterone is often considered and called male sex hormone, but in fact, it regulates sex drive and many other processes in both sexes. In men, the main production of testosterone is localized to the smooth endoplasmatic reticulum of Leydig cells in the testicles (Brown-Séquard 1889). Plasma of normal healthy women also contains about ten times lower testosterone concentration than an adult human male body, but females are more sensitive to the hormone. Half of testosterone amount in females is generated by the ovaries, the rest by the cortex of suprarenal glands (Lobotsky et al. 1964, Wu et al. 2010). Biosynthesis of testosterone occurs also in other tissues, even in some regions of the brain (Mensah-Nyagan et al. 1996, Matsunaga et al. 2002). A simplified scheme of testosterone metabolism is illustrated on Figure 1. This trajectory is essential to be mentioned, because all these metabolic steps can influence final concentration of testosterone and its effect on target tissues.

Molecular mechanism of testosterone action can vary (Fig. 2). Testosterone as well as dihydrotestosterone are ligands of the nuclear androgen receptor (Askew et al. 2007). In the classical genomic pathway, the ligand activated receptor is an important transcription factor that regulates expression of genes involved in cell proliferation, differentiation, metabolism and apoptosis (Nelson et al. 2002). For the regulation of expression protein coactivators are recruited (Estebanez-Perpina et al. 2005). Beyond the genomic

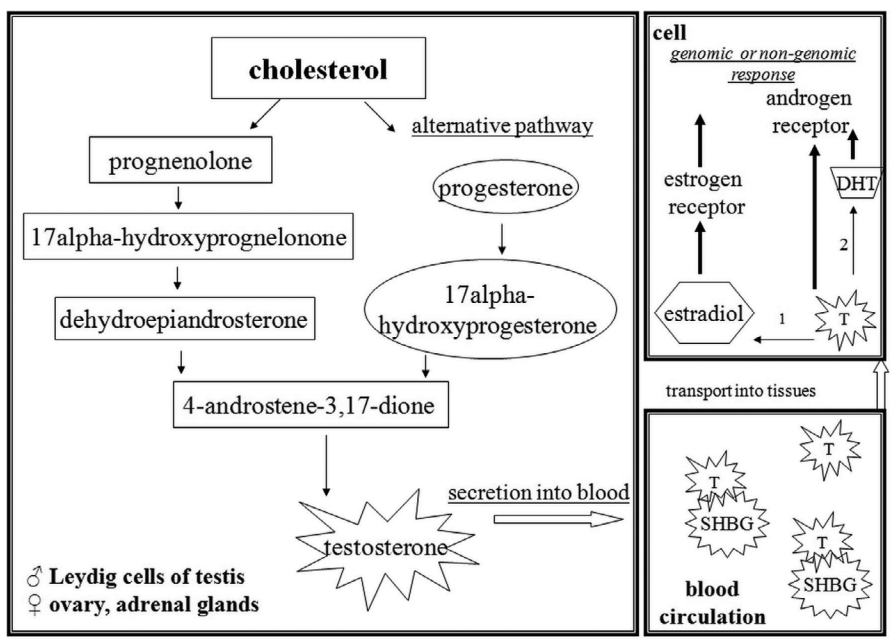

Fig. 1. Testosterone metabolism. Testosterone is a steroid hormone metabolized from cholesterol by desmolase activity. Pregnenolone is a product of this reaction and is converted to testosterone *via* intermediates 17-alpha-hydroxypregnelonone, dehydroepiandrosterone and 4-androstene-3, 17-dione (Yamazaki and Shimada 1997). In the alternative pathway, testosterone is produced with intermediates including pregnenolone, progesterone and 17-alpha-hydroxyprogesterone (Rose et al. 1997). In blood circulation, testosterone binds to sex hormone binding globulin (SHBG) and is, thus, protected from metabolic degradation but also biologically inactive. Only a small fraction of the hormone is free and active (able to bind to its receptor or to be further metabolized) (Maruyama et al. 1987). In some target tissues (adipose tissue, brain) aromatase catalyzes the conversion of testosterone to the female sex steroid hormone estradiol. The effect is then mediated *via* estrogen receptors (Carreau et al. 2003). Alternatively, 5α-reductase reduces testosterone to more a potent androgen dihydrotestosterone (DHT) which also binds androgen receptor (Askew et al. 2007, Roy and Chatterjee 1995, Shidaifat 2009).

response androgen receptor mediates also non-genomic effects (Fig. 2). This response does not involve transcription or translation, and is very rapid in comparison to so-called genomic effects. An activated androgen receptor stimulates an increase of intracellular Ca^{2+} level, activates multiple protein kinases, thereby enabling protein interactions and triggering important signaling cascades (Baron et al. 2004, Foradori et al. 2008, Li and Al-Azzawi 2009). More information about the androgen receptor, its genomic and non-genomic effects is available in a recently published review (Bennet et al. 2010).

Some cells including macrophages lack a typical androgen receptor but contain testosterone-binding sites on the surface of the plasma membrane. These receptors are functionally coupled with intracellular Ca^{2+} homeostasis. Testosterone binding stimulates Ca^{2+} mobilization that results in an increase of its intracellular levels. Membrane-associated testosterone receptors are linked with G-proteins associated with phospholipase C. Interestingly, these receptors are internalized independently on clathrin-coated vesicles and initiate transcription-independent signaling pathways (Benten et al. 1999). In neuronal membranes testosterone can also bind to a subunit of the ATPase complex and alters the functional status of ion channels (Ramirez and Zheng 1996).

Androgenic and anabolic effects of testosterone responsible for variety of morphological characteristics are well described and widely known. Some effects require conversion of testosterone to more potent androgen named dihydrotestosterone playing a pivotal role in maturation of the sex organs, particularly the penis and the scrotum during the fetal development (Toppari and Skakkebaek 1998). In puberty testosterone stimulates the growth of the genitals, development of other male secondary sex characteristics (Hiort 2002), induces growth of the prostate, hair and causes male balding (Shidaifat 2009, Trueb 2002). A number of studies were published focusing on the issue how testosterone concentrations influence target tissue and modulate the final phenotype (Hausmann et

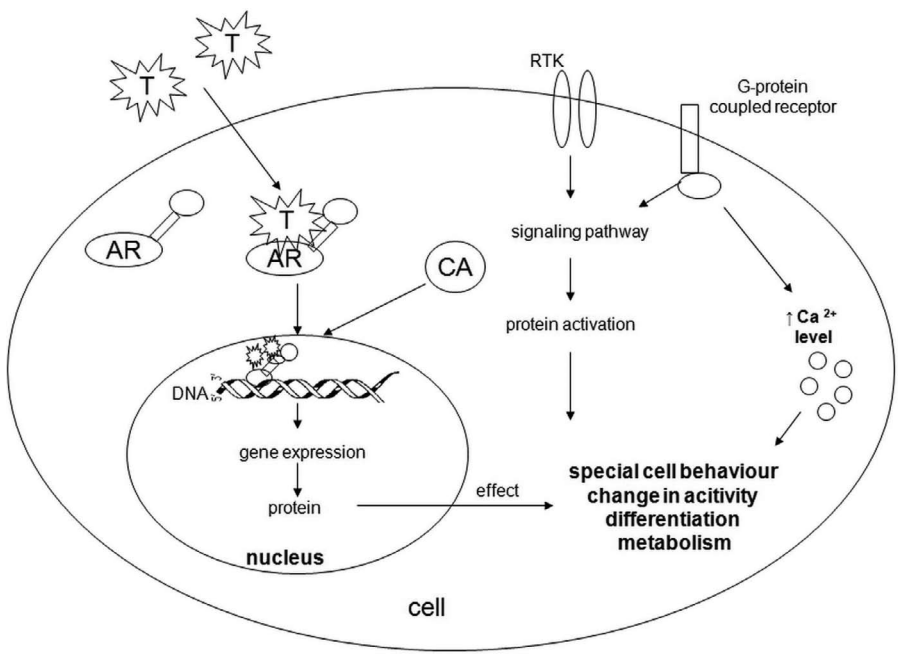

Fig. 2. Genomic and non-genomic effects of testosterone. Unbound bioactive testosterone interacts with the cytoplasmatic androgen receptor (AR). AR is also activated by dihydrotestosterone in a similar way. Ligand binding induces conformational changes of the receptor. T-AR complex forms dimers and acts as a functional transcription factor. Activated AR recognizes the androgen response element in the nucleus due its specific structure. Coactivators (CA) and RNA polymerase II are recruited for transcription initiation. Gene expression produces a pool of specific proteins that can affect cell characteristics, metabolism and activity. The non-genomic response is mediated *via* receptor-tyrosine-kinases (RTK) or G-protein coupled receptors. Subsequently, downstream signaling cascades are activated, that can result in genomic effect (activation of various transcription factors, protein activation or new protein synthesis). G-protein coupled receptors can activate phospholipase C and cause an increase of intracellular Ca^{2+}. All these processes are linked with changes in cell activity.

al. 2000, Janowsky et al. 1994, McEwen et al. 1997). On the other hand, variety of factors, emotions and brain activities influence testosterone response itself (Fig. 3), because testosterone activity is finely regulated and sensitive to endogenous and exogenous stimuli. For example, sexy thoughts increase testosterone levels in women (Goldey and van Anders 2010). Watching and participating in sexual activity induces an elevation of testosterone level in men (Escasa et al. 2010). Hormonal changes occur when falling in love. Testosterone levels are lower in men in love, while women in love have higher testosterone levels. All hormonal differences are eliminated during a long-term stable relationship (Marazziti and Canale 2004). Human competitive interactions highly influence hormonal fluctuation. The victory provokes strong emotions associated with testosterone increased (Carre and Putnam 2010). Interestingly, home victory of amateurs hockey players is associated with larger testosterone rise relative to the away victory (Carre 2009).

TESTOSTERONE AS A MODULATOR OF COGNITIVE ABILITIES, EMOTIONS AND BEHAVIOR

In men, high levels of endogenous testosterone seem to encourage dominant behavior. In some cases, dominant behavior is aggressive, but often dominance is presented nonaggressively. In other cases, dominant behavior takes the form of antisocial acting, including rebellion against authority and law breaking. It is generally believed that high levels of endogenous testosterone are associated with higher facing of the challenge and greater risk taking (Eisenegger et al. 2010, Stanton et al. 2011). Androgens can also modulate almost every aspect of sexual behavior – i.e., not only autonomic functions, but also emotional, motivational, and cognitive ones. Changes in testosterone levels influence men's judgments of women's attractiveness and complement previous findings showing that testosterone modulates men's interest in sexual stimuli. Men report stronger physical attraction (in term of mate preference) to feminity in women's faces when their testosterone levels are high (Welling et al. 2008). Ovulation in women that is linked with the peak of testosterone levels might differentially affect attention and memory processes. Women near ovulation increase their visual attention to attractive men. However, this increased visual attention is not translated into better memory (Anderson et al. 2010). Luteinizing hormone-releasing hormone (LHRH) neuronal cells possess several elements of the machinery through which sex steroids may influence LHRH dynamics and thereby, orchestrate functions *in vivo* as diverse as the onset of puberty, the timing of ovulation, and the duration of lactational infertility critical for reproduction (Poletti et al. 1994). Sex steroids achieve this indirectly, however, since LHRH neurons do not express androgen or estrogen receptors (Huang and Harlan 1993). It is now thought that kisspeptin neurons mediate the actions of sex steroids on LHRH neurons (d'Anglemont de Tassigny and Colledge 2010). The majority of kisspeptin neurons express estrogen receptor alpha and androgen receptors (Smith et al. 2005b). In females, high levels of estrogens and progesterone stimulate kisspeptin neurons of the anteroventral periventricular nucleus (AVPV) to induce the preovulatory surge of LHRH and luteinizing hormone, whereas they inhibit *KISS1* expression in the arcuate nucleus (ARC). In males, LHRH release is negatively regulated by circulating testosterone, partly through the activity of kisspeptin neurons of the ARC (Smith et al. 2005a). Although immunocytochemical and autoradiographic studies failed to detect appreciable amounts of estrogen or androgen receptor in LHRH-producing neurons, the recent finding revealed that the promoter region of the *LHRH* gene contains several steroid hormone-responsive elements indicates a possible direct effect of sex steroids on these specialized neurons (Shakil et al. 2002). Mating behavior is dependent upon both chemosensory and hormonal cues. Anatomical data suggest that these signals are transmitted through parallel pathways in separate subdivisions within brain regions (Gomez and Newman 1992). Wood and Newmann (1995) demonstrated communication between neurons receiving hormonal signals and chemosensory cues. Chemosensory cues from the vomeronasal organ and olfactory mucosa are transmitted through limbic nuclei that contain receptors for gonadal steroid hormones, including the medial amygdaloid nucleus and medial preoptic area (Wood and Newman 1995). Odor and hormonal signals must be integrated in the brain for copulation to occur. Impaired transduction of chemosensory cues in absence of gonadal steroids prevents activation of neurons in certain brain area of castrate male resulting in abolish of mating behavior (Wood and Coolen 1997). Animal experiments in mice pointed out that gonadal hormones may affect the response of vomeronasal organ neurons to chemosignals by altering

levels of the receptors to which they bind and therefore are also implicated in the regulation of sexually dimorphic behavioral and neuroendocrine functions (Alekseyenko et al. 2006).

Although intelligence in general is similar in men and women, cognitive skills in both sexes differ in detail. During mental rotation tasks men preferentially use the right hemisphere and are more lateralized, while women use both hemispheres and present lower lateralization. In general, men are better in logical reasoning and abstract mathematics. Females on average outperform males in cognitive empathy, verbal communication and emotional intelligence. The male sex hormone testosterone involved in brain organization is believed to be involved in these differences (McKeever 1995, Hines 2010).

Behavioral differences can be detected even in childhood during playing. Boys prefer different toys, activities and games in comparison to girls of the same age. Cognitive skills and behavior are the result of contemporary action of genetic, environmental factors and their interaction influencing endogenous factors, such as testosterone levels. Girls that are affected by higher fetal testosterone levels display a typical male pattern of play (Auyeung et al. 2009, Hines et al. 2002). Recent study of children in the age of 18–24 months revealed a positive association between high levels of fetal testosterone and autistic traits (Auyeung et al. 2010).

Mental rotation is one of the cognitive domains often studied in the context of gender specific testosterone effect. It is associated with spatial processing. Shepard and Metzler (1971) introduced the concept of mental rotation into cognitive science. It has become one of the best-known experiments in the field. In a mental rotation test, the subject is asked to compare two 3D objects and state if they are the same image or if they are mirror images. The subjects will be judged on how accurately and rapidly they can distinguish between the mirrored and non-mirrored pairs (Shepard and Metzler 1971). Men generally outperform women in mental rotation related to different neurobiological processes, task-solving strategies or different brain architecture (Hugdahl et al. 2006). Steroid hormone exposure in males during early development and during puberty plays a prominent role in sexually dimorphic brain formation, possibly contributing to sex differences in some cognitive parameters and behavioral features (Williams and Meck 1991, Fitch and Denenberg 1998, Goel and

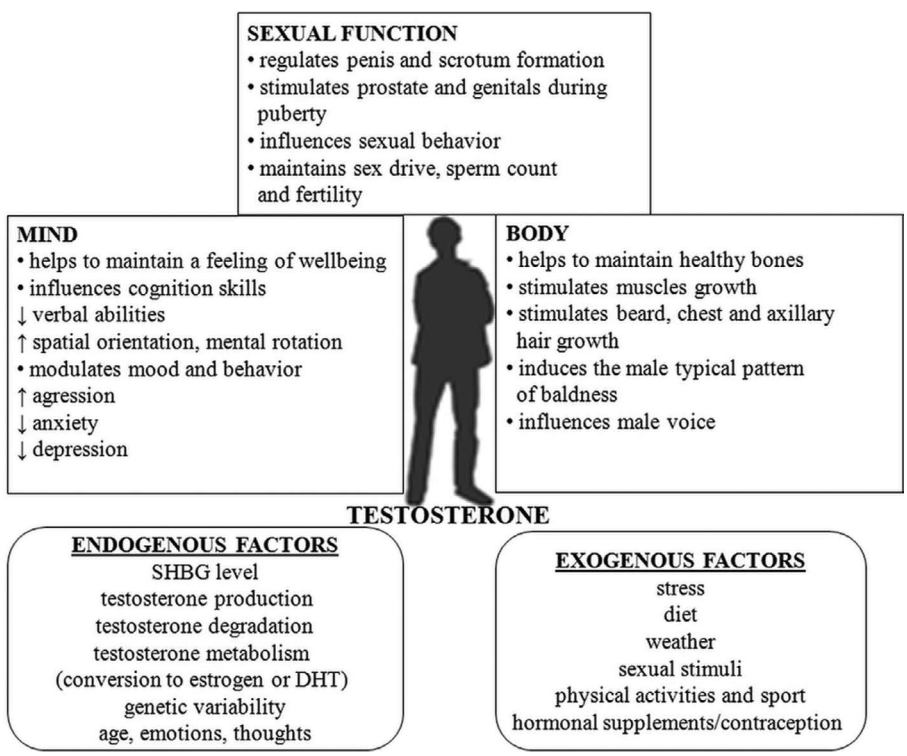

Fig. 3. Schematic illustration of testosterone activity with factors modulating its levels and effects. **(↑)** stimulation; (↓) attenuation. Androgen activity is dependent upon testosterone level influenced by various factors. Testosterone influences body morphology and various functions.

Bale 2008). It has been shown that women with higher testosterone levels outperform women with low testosterone levels in mental rotation and spatial visualization. On contrary, in men a negative correlation between spatial abilities and testosterone level was found (Ostatnikova et al. 2002). Abnormally high testosterone levels are linked with poor spatial ability but better verbal fluency. This paradoxical result indicates that increasing testosterone levels do not necessarily lead to an amplification of male characteristics. It seems that there is something like an optimal level of testosterone for certain cognitive abilities (O'Connor et al. 2001). Testosterone, at least in pre-pubertal children, seems to be related also to general intelligence quotient (IQ). Boys with an average IQ values have significantly higher salivary testosterone levels when compared to intellectually gifted or mentally challenged boys. It is currently unclear whether genetic and/or metabolic factors are responsible for the observed differences (Ostatnikova et al. 2007).

Cognitive abilities seem to be sensitive to sex hormone fluctuations (Gouchie and Kimura 1991, Heil et al. 2011). Individuals with congenital adrenal hyperplasia exposed to higher androgen levels *in utero* may manifest long-term changed more masculine pattern in cognitive function when compared to healthy population under the influence of increased prenatal androgen exposure (Maheu et al. 2008, Mueller et al. 2008). Studies in 5α-reductase deficient subjects, a unique model to study the effect of a selective inherited deficiency of dihydrotestosterone on cognitive patterns, indicate that the 5α-reductase deficient subjects have a higher performance IQ than would be expected in males from this kindred and show relatively better right hemisphere function (Lawson and Inglis 1983). Some cognitive functions are responsive also to current testosterone level changes. It is well documented that spatial ability varies in women during the menstrual cycle with its maximum in the periovulatory phase (Ostatnikova et al. 2010) related to maximum peak of salivary testosterone (Celec et al. 2002). Plasma testosterone fluctuations during the menstrual cycle cause a significant difference in spatial ability with high scores during the menstrual phase and low scores during the midluteal phase. Testosterone in contrast to estradiol has a strong positive influence on mental rotation performance (Hausmann et al. 2000). Hormonal contraception with androgenic properties improves visuo-spatial abilities (Griksiene and Ruksenas 2011). But contrastingly, administration of testosterone in young women leads to a significant impairment in their cognitive empathy (van Honk et al. 2011). Study of human female-to-male transsexuals brings the evidence that testosterone administration for at least 6 months improved significantly their performance on a visual memory task that supports the evidence of activating effect of testosterone (Gomez-Gil et al. 2009). Aging in men and women is associated with a decline of bioavailable testosterone levels. However, unlike menopause when estradiol falls rapidly to very low levels, testosterone production declines slowly in healthy men. Men in their seventies have approximately 40% lower testosterone than men in their twenties (Davidson et al. 1983). At the same time, more sex hormone binding globulin is produced and, therefore, the bioavailable fraction of testosterone is reduced even further. Age related loss of testosterone is tightly linked with cognitive decline and possibly dementia (Driscoll and Resnick 2007). Men with Alzheimer disease have lower testosterone levels prior to their diagnosis in comparison to controls (Hogervorst et al. 2003). Studies in aging men show that bioavailable testosterone levels might influence cognitive performance by modulating attention control (Martin et al. 2009). Low estradiol concentration and high testosterone levels despite older age predict a better cognitive performance in men. Whether age-related decline in cognition might be reversed by hormonal replacement therapy is not clear despite a number of published studies (Wolf and Kirschbaum 2002).

Such findings suggest a pivotal role of hormonal influence on certain cognitive domains in humans, mirroring results from research on animals (Konkle and McCarthy 2011, Korenbrot et al. 1975). Hodosy and coauthors (2010) analyzed the correlation between testosterone levels and spatial memory in male and female rats. Intramuscular administration of testosterone improves spatial memory in female rats tested in the Morris water maze. Surprisingly, high doses of testosterone in male rats cause decrease in reference memory. These findings suggest that testosterone affects spatial memory in a dose and gender dependent manner (Hodosy et al. 2010). There are also several studies confirming that castration and subsequent testosterone deprivation impair spatial working memory retention (Daniel et al. 2003, Daniel and Lee 2004, Sandstrom et al. 2006). Testosterone injections reduce the number of working memory errors of castrated

male rats. Certain doses of testosterone increase preservative behavior in a reversal-learning task indicating positive activational effects on spatial learning and memory, but the duration of testosterone replacement and the nature of the spatial task modify these effects (Spritzer et al. 2011). Testosterone, but not dihydrotestosterone, improves working memory and decreases hippocampal NGF (neural growth factor) protein in aged male rats. Androgen treatment lowers circulating estradiol levels in aged male rats, suggesting a feedback to the hypothalamic pituitary. Conversion to estrogen may, thus, not be the underlying biological mechanism of effects of testosterone on memory. The ratio of estradiol to testosterone, or the actions of the aromatase enzyme itself, may be responsible for the observed effects. These data support the hypothesis that testosterone therapy in aging individuals may provide positive effects on cognition and that neural regions that are linked to cognition, such as the hippocampus and/or entorhinal cortex, may be involved in such effects (Bimonte-Nelson et al. 2003, Bimonte et al. 2003).

Testosterone is widely discussed as a cognitive enhancer. Its effects are not completely understood and have received attention because of potential therapeutic applications. Parallel studies in humans and animal models are not simple. Animal studies enable to induce androgen deprivation or competitive blockage of testosterone function. These circumstances cannot be easily translated into human analyses, therefore evaluating of the exact molecular actions how testosterone administration influences cognitive functions in humans remains the challenge. Particularly, it is problematic to distinguish whether improvement in cognitive skills after testosterone replacement therapy can be explained with classical genomic effect or rapid non-genomic pathway.

TESTOSTERONE EXPOSURE AND BRAIN ORGANIZATION

We are far from a complete understanding of the detail molecular mechanism behind the effects of testosterone and other steroids on brain structure and function. Sex steroids influence myelination

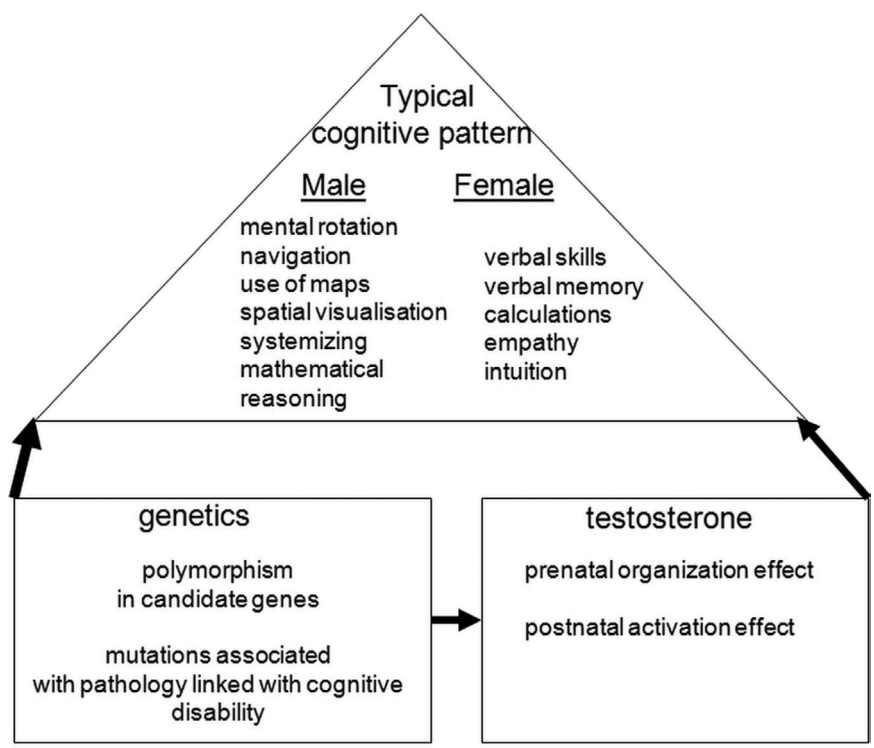

Fig. 4. Schematic link between genetic factors, testosterone and cognitive skills. Cognitive performance is influenced by genetic factors. Polymorphisms in candidate genes can modulate the activity of the final protein product. Polymorphisms of the androgen receptor change its activity as a transcription factor. Mutations in the androgen receptor gene cause androgen insensitivity syndrome. Somatic mutations in genes involved in testosterone metabolism can influence biosynthesis of testosterone and the concentration of its bioavailable fraction.

through their direct impact on glial cells, increase synapse number and dendritic branching (Cook et al. 2002, Romeo et al. 2004). Testosterone was found to change gene expression in neurons modulating their possible responses to incoming signals (Fink et al. 1988). Several studies confirmed the effects of testosterone on formation and loss of synaptic connections, cells growth, migration, apoptosis or neurotransmitter metabolism modulating neuronal activity (Matsumoto 2001, 2005, MacLusky et al. 2006, Zehr et al. 2006). All these processes are crucial for remodeling of brain structures (Lustig 1996). Traditionally, two types of hormonal action on the brain have been distinguished. Organizational effects are irreversible and act on the CNS to predetermine neural pathways. They can make neurons more sensitive to the later activational effects of testosterone that occur at any time of the life. Activational effect means modulation of neural pathway affecting certain behavior (Cohen-Bendahan et al. 2005, Hines 2010, Ngun et al. 2010, Von Horn et al. 2010).

In humans, a critical period for organization of the brain is thought to be between weak 8 and 24 of gestation (Collaer and Hines 1995). During this period testosterone levels are high. Testosterone levels peak in the fetal serum between weeks 12 and 18 of pregnancy (Finegan et al. 1989). This developmental period is essential for normal CNS function, brain masculinization in male fetuses and neurological health. The first trimester is as important as the foundation and frame of the house. If it is disrupted, the integrity of the whole house will be compromised (Mrazik and Dombrowski 2010). This metaphor illustrates the real situation in human body and brain development (Mrazik and Dombrowski 2010). The theory of Geschwind and Galaburda (1985) claims that intellectually gifted children are influenced by higher androgen levels during intrauterine development. High testosterone concentrations during prenatal life have effects on the differentiation of the central nervous system, as they attenuate the growth of the left hemisphere. The resulting right hemisphere dominance is associated with enhanced lateralization, left handedness, spatial orientation and logical reasoning (Geschwind and Galaburda 1985). All these features are supposed to be more common or better developed in intellectually gifted children (Geschwind and Galaburda 1985). The redirection of neuronal migration away from areas responsible for language in favor of the inferior parietal region of the cortex might lead to apparent language based disability such as dyslexia. Albert Einstein was an example of an individual who experienced an overdeveloped inferior-parietal region contributing to his extraordinary mathematical capabilities. On the other hand, Einstein did not speak until age 3 and suffered from language deficits (Anderson and Harvey 1996). This phenomenon of genius and disability at the same time can be explained by prenatal exposure to higher testosterone levels in uterus bringing the evidence that testosterone can be considered very important etiologic factor in brain development and modulation of certain cognitive domains.

The second peak of testosterone takes place in the first 3 months after birth. At the end of the pregnancy, when a-fetoprotein declines, the fetus is more exposed to estrogens from the placenta, which inhibits the hypothalamus–hypophysial–gonadal axis of the child. This inhibition is lost when the child is born, which causes a peak in testosterone in boys and a peak in estrogens in girls (Quigley 2002). The testosterone level in boys at this time is as high as it will be in adulthood. Also at this time the testosterone level is a factor higher in boys than in girls. The role of this testosterone evaluation is not completely clear but it is supposed to fix the development of structures and circuits in the brain for the rest of a person's life (Swaab 2007).

The brain during puberty is sensitive to the organizational effect of gonadal hormones (Ahmed et al. 2008). Animal studies showed that pruning of dendrites in combination with axonal changes are very frequent during puberty (Cooke et al. 2007). Prepubertal gonadectomy in rats results in reduction of cells within sexually dimorphic area of hypothalamus and amygdala and increases the number of androgen receptors in amygdala (Romeo et al. 2000, Ahmed et al. 2008). Neuroimaging studies in humans have shown dynamic changes in brain during puberty. Subcortical gray matter areas included hypothalamus, thalamus, amygdala, hippocampus, known for their high density of sex steroid receptors, show a significant susceptibility to reorganization induced by sex steroid hormones activity during pubertal development (Gogtay and Thompson 2010, Bramen et al. 2011). Testosterone predicts white matter increases in whole brain and in areas connecting the frontal and temporal cortices. Maturation of these regions is implicated in typical adolescent behaviors including social development, enhanced reward sensitivity and reduced cognitive control (Blakemore 2008, Olson et al. 2009).

Literature provides evidence for permanent sex hormones effect on brain and behavior during early development. Brain remains sensitive to the effects of sex hormones into adolescence, undergoing structural changes as a result of hormone exposure. But there are still many remaining questions including the exact mechanism of testosterone action and its regulation, neural substrates for hormone effects or relationship between prenatal and pubertal period. Another challenging issue remains to reveal biological determinant of the intellectually gifted brain. What is the difference between precocious and average brain? What biological force is responsible for the exceptional abilities? There are several hypotheses supposing testosterone to be important in the development of cognitive giftedness. Convincing evidence and the exact mechanism of action are still missing.

SEXUAL DIMORPHISM IN BRAIN ORGANIZATION

Understanding of mechanisms that give rise to differences in the behavior of nonhuman animals may contribute to the understanding of sex differences in humans. In vertebrate model systems, testosterone accounts for most known sex differences in neural structure and behavior. The sex-related morphological differences of many brain nuclei are mainly determined by the hormonal environment present during embryonic development. It is believed that during the intrauterine period the fetal brain develops in the male direction through a direct action of testosterone on the developing nerve cells, or in the female direction through the absence of this hormone surge (Morris et al. 2004, Hines 2010).

Animal studies with rats pointed out that nucleus of preoptic area implicated in male copulatory behavior present sexual dimorphism. Perinatal aromatized androgen decreases neural apoptic rate in males, therefore it is 2.6 times larger when compare to females. Treating newborns females with testosterone reduces the number of dying cells resulting in larger sexual dimorphic preoptic area (SD-POA) (Davis et al. 1996). In contrast, hormone manipulations in adulthood have no impact on the volume of this nucleus (Gorski et al. 1978). Sexually dimorphic region are not always larger in males. Anteroventral periventricular nucleus (AVPV), part of hypothalamus associated with regulation of ovulatory cycles, is larger in females with a higher cell density in both mice and rats. In this case apoptosis in males is contrastingly enhanced due to prenatal action of metabolized testosterone resulting in increased degeneration of cells in this region (Simerly 2002). The opposing responses of SD-POA and AVPV to testosterone indicate that molecular background in these different target cells is different. The spinal nucleus of the bulbocavernosus (SNB) important for male sexual behavior control also displays sexual dimorphism relied on apoptosis. Male rats have larger and more motor neurons than females. Neural cells die in females around the time of birth unless they are exposed to testosterone. Although SNB motor neurons posses androgen receptor, effect of testosterone is primarily to prevent death of the target muscle cells, which then secondarily protect neurons from apoptosis and keep them alive (Nordeen et al. 1985).

Taking together testosterone or its metabolites can affect the rate of apoptosis acting *via* the specific receptor. In one type of cells apoptosis can be stimulated, in another target system it can be suppressed as a consequence of modulation of anti-apoptic gene *Bcl2* expression (Morris et al. 2004). Testosterone also acts on neurons to cause them to release chemo-attractants promoting sexually dimorphic innervations pattern. Steroid can induce one population to masculine the other *via* the synapse communication (Ibanez et al. 2001). According to the callosal theory, prenatal testosterone mediates early axon pruning in callosal tissue, and thus the more testosterone a brain is exposed to in uterus, the more lateralization there is, evidence of less lateralization in females supports this hypothesis (Witelson and Nowakowski 1991). Increased androgen sensitivity of preprogrammed brain structures is believed to result not only in better ability to undertake 3-dimensional spatial rotation, but also in a host of behavioral changes such as higher risk taking, search persistence, heightened vigilance, and faster reaction times (Chura et al. 2010).

Some of brain structures can be sexually differentiated in adulthood (Cooke et al. 1999). Posterodorsal medial amygdala (MePD) strongly associated with emotions, decision making, male sexual arousal, is strongly dependent on adult testosterone. MePD volume is 1.5 times larger in males in rats and mice due to activational effect of circulating androgens. Testosterone in adulthood manipulations can completely reverse sex differences (Cooke et al. 2003). Neuroimaging studies highlight the activational effects of gonadal hormones on the amygdala and prefrontal cortex also in humans.

Table I

Genetic polymorphisms associated with testosterone metabolism

Gene	Protein	Polymorphism	Consequence	Reference
NR3C4	androgen receptor	(CAG)n in exon 1	Number of repeats influences the function of the androgen receptor as a transcription factor. Long CAG repeats are associated with a decreased transactivation activity.	(Irvine et al. 2000) (Chamberlain et al. 1994)
CYP19	aromatase	C to T substitution in exon 10	Substitution is characterized by higher aromatase expression from an alternative promoter.	(Kristensen et al. 2000)
SRD5A2	5α-reductase	Substitution A49T Alanine in codon 49 is substituted with threonine	Treonine allele in *SRD5A* gene leads to fivefold increase of reductase activity.	(Makridakis et al. 1999)
SHBG	sex hormone binding globulin	Substitution Asp327Asn Aspartic acid in codon 327 is replaced by asparagine	Asn allele in the *SHBG* gene may be related to increasing blood SHBG levels.	(Cui et al. 2005)
ESR1	estrogen receptor alpha	*Pvu*II polymorphism Transition T to C in exon 1	Polymorphism enhances estrogen receptor activity.	(Khosla et al. 2004)

Activational effects strongly contribute to the sex differences in the neurocircuitry underlying the regulation of emotion and affect (Goldstein et al. 2010). Recent studies indicate that progesterone and testosterone have diverging effects on the communication between the amygdala and prefrontal cortex (van Wingen et al. 2010), which may contribute to sex differences in the vulnerability to various psychiatric disorders. Women suffer more from mood and anxiety disorders, whereas men suffer more from impulse-control and substance use disorders (Kessler et al. 2005). Swaab and his colleagues published several remarkable papers about dimorphism of brain structures in relationship to gender identity (Swaab and Hofman 1990, Garcia-Falgueras and Swaab 2008). They were the first who showed a female brain structure in genetically male transsexuals and supported the hypothesis that gender identity develops as a result of an interaction between the developing brain and sex hormones (Zhou et al. 1995).

Future may bring answer to the question about what genes are directly regulated by androgen action to induce sexual dimorphic morphology of the brain, unique gender identity, sexual orientation and behavior. Which of them directly modulated by testosterone or its metabolites are crucial for initiation of brain differentiation and masculinization?

THE ROLE OF GENETIC FACTORS IN MODULATION OF STEROID ACTIVITY

Individual behavioral traits or specific cognitive abilities are the result of a cooperation of genetic, hormonal

and environmental factors (Fig. 4). Testosterone activity is influenced by variants in genes involved in its metabolic processing. Main candidates possibly considered modulators of testosterone effect in relation to cognitive function are summarized in Table I. Gene for aromatase of testosterone (*CYP19*) is located on chromosome 15. A genetic variant with C substituted by T in exon 10 in 3′-UTR region is associated with higher aromatase production and increased risk of breast cancer (Kristensen et al. 2000). *SRD5A2* gene encoding 5α-reductase is localized on the chromosome 2. Substitution of alanine with threonine in codon 49 is linked with increased activity of reductase (Makridakis et al. 1999). Substitution A49T in enzymatic product of *SRD5A2* gene occurs in intellectually gifted children (boys and girls) more frequently in comparison with control population. Similarly, C-T substitution in exon 10 in the aromatase gene was detected more frequently in intellectually gifted children (boys and girls) when compared to control group. This genetic background influences aromatase and reductase activity, testosterone level and might enhance its androgenic effects on cognition (Holešová et al. 2006).

Androgen receptor (AR) can be considered a major modifier of speed of neural transmission (Manning 2007). Gene for AR is located on the X chromosome and consists of eight exons. AR protein can be divided into several domains with specific function (Fig. 5). For detailed information, excellent review about AR is available (Bennet 2010). A polymorphic three-nucleotide (CAG)n repeat in exon 1 encodes a polyglutamic tract (Choong and Wilson 1998). Normal variation is in range of 11 to 35 repeats (Greenland and Zajac 2004). Interestingly, a loss-of-function mutation of AR is not linked with intelligence impairment, but a short repeat in the AR is linked with mental disability and retardation (Kooy et al. 1999). Massive expansion of (CAG)n, on the other hand, is also associated with severe pathology in the form of the Kennedy disease (Greenland et al. 2004). Higher but still normal number of repeats in exon 1 of the AR gene has been shown to affect some personality traits (Westberg et al. 2009). In the range of normal variation low number of repeats causes higher transactivational activity of AR and, thus, higher sensitivity to androgens (Tut et al. 1997). Comparison of sequences of the AR gene from five different primate species reveals that there is an evident increase in number of repeats in the primate evolution to humans. This expansion has a direct effect on AR structure, activity and can be also an important phenomenon in the evolution of intelligence and cognition (Choong et al. 1998). Remarkable population differences in repeats were detected using X-chromosome analyses. Men of African descent have a mean number of (CAG)n repeats between 16.7–17.8. Men of European origin have a mean of 19.7 and men of Asian descent 20.1 repeats. These findings positively correlate with IQ value measured in meta-analyses (Kittles et al. 2001). On the other hand, evaluation of intellectually

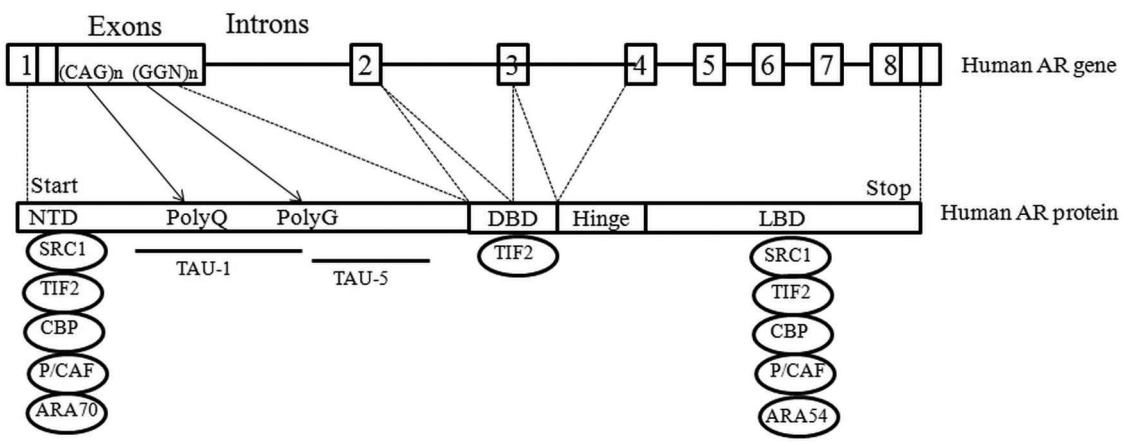

Fig. 5. Scheme of human androgen receptor (AR) gene and AR protein. The gene encoding AR has eight exons and produces a cDNA approximately 2760 nucleotides in length and a protein of approximately 920 amino acids. The AR protein consists of four structurally and functionally distinct domains, N-terminal transactivation domain (NTD), DNA binding domain (DBD), a small hinge region and a C-terminal ligand-binding domain (LBD). Locations of transcriptional activation units (TAU-1, TAU-5) and some of important coactivators are also illustrated.

gifted pre-pubertal children shows that there are no significant differences in the number of repeats between intellectually gifted boys and controls (Holešová et al. 2006).

Many coregulators are recruited to AR (Fig. 5) with and without bound ligand influencing DNA binding, nuclear translocation, chromatin remodeling, binding interruption of other co-regulators, AR stability, and bridging AR with the basal transcriptional machinery (Shen et al. 2005, Chmelar et al. 2007).

Although knowledge of AR structure, functional mechanisms within cell, and its molecular biology is extensive, for complete understanding of AR function certain issues need to be clarified. Studies on the androgenic effects on target tissues are difficult to interpret due to complex molecular background, plenty of coregulators and corepressors affecting AR activity. Several animal studies use androgen receptor inactivation using competitive inhibitors to prove the role of AR in physiology and pathology. However, it is unknown what the exact cellular response is after androgen receptor blockage or how interacting partners exactly behave. Another complicating fact is the possible switch into the non-genomic pathway that is not fully characterized and understood.

PRENATAL ANDROGEN EXPOSURE AND 2D/4D RATIO

For comprehensive analysis of testosterone effect, prenatal influence is needed to be considered. Although it is not easy to measure hormones during prenatal development, several researchers have successfully examined hormones in amniotic fluid and then related these hormones to behavior, this method was first proposed and used by Finegan and colleagues (1989). Because such studies are difficult to conduct, there has been considerable interest in studying indirect indicators of prenatal testosterone exposure in relation to contemporary behavior in children and adults. These indicators include sharing the uterine environment with markers such as fingerprint patterns and length ratio of the second to fourth finger (2D/4D ratio) (Manning et al. 1998, Lippa 2006, Malas et al. 2006,).

Male fetuses undergo intensive testosterone production during the prenatal period. The peak in human male testosterone production occurs between 10^{th} and 18^{th} week of gestation (Maccoby et al. 1979). In this time of early testosterone exposure, sex steroids directly affect not only the brain but also the bone length by influencing the development of the phalanges and the metaphyseal growth. In the metaphyseal tissues, steroids act *via* estrogen receptor alpha and beta, as testosterone is locally aromatized (Ben-Hur et al. 1997, Weise et al. 2001). Genetic analyses of the androgen receptor short tandem repeat polymorphism revealed that lower but still normal number of CAG repeats enhancing androgen effect is associated with lower 2D/4D ratio (Ding et al. 2004). Other studies did not find any relationship between polymorphism in AR and the digit ratio (Hurd et al. 2010). In addition to hormonal regulation, there is a genetic basis contributing to the differentiation of the digit ratio pattern. Particularly *HOX*a and *HOX*b genes strongly expressed in gonads are essential for differentiation of the genital bud and digit growth. Sharing of causal factors in digit and gonad differentiation supports the hypothesis that patterns of digit formation can be used as a marker for prenatal sex hormone concentration.

The length of the fourth digit (ring finger) is thought to be an index of prenatal testosterone exposure relative to the length of the second digit (index finger), which is thought to represent an index of prenatal estrogen exposure (Manning et al. 1998, Manning and Taylor 2001, Manning and Fink 2008). According to several studies, 2D/4D ratio can be considered a relevant indicator of prenatal hormonal environment (Finegan et al. 1989, Manning et al. 1998, 2000, Manning and Taylor 2001, Kempel et al. 2005, Manning and Fink 2008, Manson 2008, Hurd et al. 2010). This parameter is believed to be fixed *in utero*. It can be reliably measured as early as in 2 years of age and is stable during the entire life, not affected by pubertal growth (Manning et al. 2000). The relative length of the second and the fourth finger is sexually dimorphic. In males the 2D/4D ratio is lower having the mean of 0.98 caused by longer 4D. Females have a higher 2D/4D value with mean of 1.00 explained by equal lengths of second and fourth finger. Except sexual dimorphism, remarkable variability was reported in large-scale population studies. In mixed race samples, people of African origin had lower 2D/4D at all ages, but significant differences were detected between nationalities and ethnic groups (Manning et al. 2000). Possible explanation is the different androgen exposure *in utero* (Manning et al. 1998). Supporting data come from studies on congenital adrenal hyperplasia.

Higher androgen exposure caused significantly lower 2D/4D when compared to healthy controls (Brown et al. 2002). Animal studies on bird eggs confirmed the prenatal androgen effect on 2D/4D (Romano et al. 2005).

The 2D/4D digit ratio was found to be associated with many physiological, behavioral and cognitive parameters that are sexually dimorphic and influenced by hormonal activity, even the sexual orientation (Fig. 6). Homosexuals of both sexes have a lower 2D/4D ratio when compared to heterosexuals suggesting higher androgen levels prenatally (van Goozen et al. 2002, Rahman and Wilson 2003). Finger ratio was measured in association with reproductive success in healthy men and women. For men, there is a negative association between low 2D/4D and higher number of children or sperm counts. Women display positive relationship between higher 2D/4D and fertility (Manning and Fink 2008). Very high feminine 2D/4D can be a risk factor for breast cancer (Belcher et al. 2009, Devine et al. 2010). On the other hand, atypically low digit ratio is believed to be associated with autism spectrum disorders (Bloom et al. 2010, Krajmer et al. 2011). It is suggested that prenatal testosterone levels promote development and maintenance of traits useful in male fighting sports related to aggressiveness. Digit ratio 2D/4D is negatively associated with sport success in men (Manning and Taylor 2001). Low 2D/4D is also related to higher sport abilities in females (Paul et al. 2006).

In studies focused on digit ratio in relation to spatial orientation, many contradictions were found. Women exposed to higher prenatal androgen levels have lower 2D/4D (man-like) and perform better in spatial test and numerical tasks than women with a higher digit ratio (woman-like) (Kempel et al. 2005). In contrast, in males improvement in spatial ability occurred after a decrease in circulating testosterone levels. In the normal range of testosterone levels, feminine 2D/4D in males is linked with best results in visual spatial tasks (Sanders et al. 2002). A recent study investigating implications for the relationship between prenatal testosterone and academia shows social scientists of both sexes have a ratio consistent with the male norm (0.98) whilst scientists have a digit ratio consistent with the female norm (1.00). Both of these findings propose that the relationship between the 2D:4D ratio and visuo-spatial ability may reveal a U-shaped curve or other non-linear relationship (Brosnan 2006). They provoke also some speculations that 2D/4D can be related to spatial preferences rather than ability *per se* (Valla and Ceci 2011). Despite the 2D/4D is consider to be a relevant indicator of prenatal hormonal profile, recent studies brought inconsistent or controversial results that are difficult to interpret (Forstmeier et al. 2010, Medland et al. 2010, Valla and Ceci 2011). In some studies low 2D/4D on the right hand and high 2D/4D on the left hand are used as predictors of higher prenatal androgen levels. Data from the right hand are

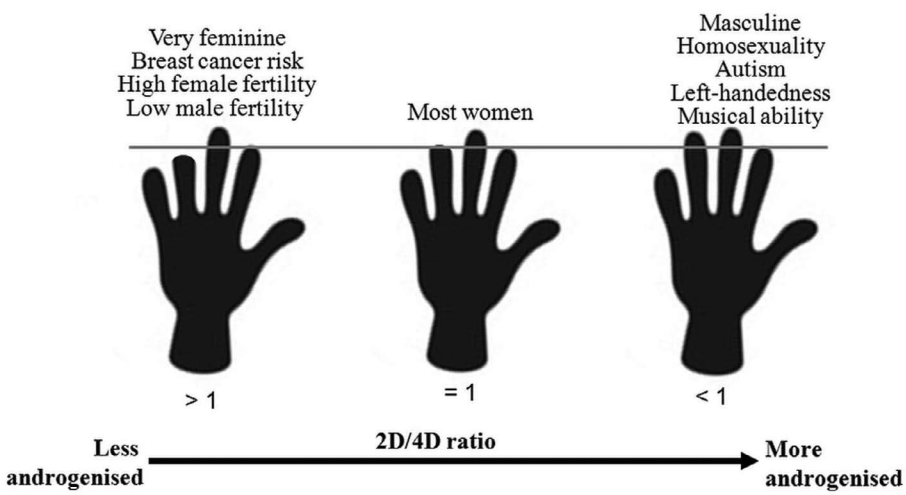

Fig. 6. Schematic illustration of relative finger lengths and possible association with typical physical features. Physical characteristics that develop in distinctly masculine and feminine ways are mostly caused by sex hormones**.** High prenatal testosterone exposure leads to masculine 2D/4D digit ratio (lower than 1). Female undergo less androgenisation that results in 2D/4D digit ratio higher than 1. Finger lengths are associated with some cognitive abilities and also with risk for disease development.

argued to be more sensitive to the effects of prenatal testosterone exposure (Manning et al. 2000). Another study claims that 2D/4D analyses are more consistent on the left hand (Von Horn et al. 2010). Due to these discrepancies in many analyses an average 2D/4D ratio of both hands was used (Brosnan 2008). Differences in digit ratios could arise if bones from different fingers are differentially receptive to sex steroids due to differences in receptor activity, aromatase activity, or different conditions for interaction between steroid receptors and growth factors. 2D/4D negatively correlated with math-intensiveness of college major in females, but not males. According to these results, there is a possibility of alternative sexually differentiated pathway including different trajectory and timescale of development, so bones differ in their temporal patterns of growth (Valla et al. 2010, Valla and Ceci 2011).

Regarding the organizational theory of brain, it is strongly believed that testosterone during prenatal development is essential biological force influencing cognitive abilities and intelligence. It could be interesting to investigate 2D/4D in intellectually gifted individuals and possibly find correlations between prenatal hormonal profile, actual testosterone levels and cognitive and behavioral characteristics to support the hypothesis about testosterone involvement in giftedness development. Animal studies which enable prenatal hormonal manipulations can potentially help to clarify what is the prenatal testosterone exposure mechanism. How exactly can prenatal hormonal environment be reflected into finger ratios or exceptional individual abilities? Why are there some inconsistencies in left and right hand or gender differences shown is some studies?

CONCLUSION

Testosterone is a hormone with many essential roles in the development of morphological, physiological and cognitive traits. Hormonal effects and their regulation very likely influenced evolution of humans in a substantial way. Research on testosterone metabolism and androgen signaling in relation to cognition is indeed interdisciplinary linking evolution, psychology, neuroscience with molecular genetics, biochemistry and endocrinology. The high number of scientific teams worldwide focusing on this area indicates that there are still a lot of aspects that remain unclear and wait to be discovered.

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