



Review

Molecular basis of androgen action on human sexual desire



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ARTICLE INFO

Article history:

Received 18 May 2017

Received in revised form

7 September 2017

Accepted 7 September 2017

Available online 8 September 2017

Keywords:

Sexual desire

Androgen

Testosterone

ABSTRACT

Reproduction is a fundamental process for the species maintenance and the propagation of genetic information. The energy expenditure for mating is overtaken by motivational stimuli, such as orgasm, finely regulated by steroid hormones, gonadotropins, neurotransmitters and molecules acting in the brain and peripheral organs. These functions are often investigated using animal models and translated to humans, where the androgens action is mediated by nuclear and membrane receptors converging in the regulation of both long-term genomic and rapid *non*-genomic signals. In both sexes, testosterone is a central player of this game and is involved in the regulation of sexual desire and arousal, and, finally, in reproduction through cognitive and peripheral physiological mechanisms which may decline with aging and circadian disruption. Finally, genetic variations impact on reproductive behaviours, resulting in sex-specific effect and different reproductive strategies. In this review, androgen actions on sexual desire are evaluated, focusing on the molecular levels of interaction.

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1. Introduction

Sexual desire is a biological process involving steroid hormones acting in the brain of two sexually distinct organisms and,

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leveraging on sexual reward, it is finalized to reproduction (Pfaus et al., 2003). The sexual intercourse is motivated by orgasm, which can be explained as an evolutionary strategy to drive individuals toward copulation and conception, focusing on maximization of the reproductive success (Fleischman, 2016). However, in humans and other primates, orgasm and sexual arousal may be uncoupled from the reproductive forms of sexual behaviour and used to orientate social interactions and emotional states (Wrangham, 1993). Sexual desire represents the first step in this fine mechanism of attraction, which relies on steroid hormones, neurotransmitters, vasoactive agents and other molecules acting through specific receptors, at both the brain and peripheral level (Rosenthal, 2016). Specific chemo-affinities are key players of this game, aiming to maximize partner attraction and selection, as well as physiological sexual functions. Individuals' genotype may be an important factor modulating the hormonal milieu and, finally, sexual behaviours and reproduction (Gunst et al., 2015).

In this article, we reviewed the androgens action on sexual desire, paying attention to molecular levels of interaction.

2. Sexual desire

2.1. Physiology of sexual desire

Sexual desire identifies a complex process, involving both cognitive and peripheral physiological mechanisms, leading to sexual arousal (Basson, 2002; Rupp and Wallen, 2008). The latter defines the cerebral activation occurring in both male and female, aiming to prepare genital organs for copulation (Motofei, 2009). Proper sexual stimuli activate the cognitive state, in which they are appraised and categorized as sexual (Rupp and Wallen, 2008). In this phase, autonomic cerebral centres are activated by somatic afferent pathways (Motofei and Rowland, 2005) and neural activity increases in specific cortical areas, such as inferior right frontal and inferior temporal cortex, anterior cingulate, insula area and hypothalamus (Redoute et al., 2000; Brunetti et al., 2008). Neuroimaging studies revealed the complex network between psychological and physiological processes during sexual arousal, highlighting sex-specific differences (Poepl et al., 2016). Despite similar activation level of occipitotemporal, dorsal anterior cingulate and lateral prefrontal cortex was observed in both sexes, the functional neuroanatomy of sexual processing is slight different (Poepl et al., 2016). In particular, men displayed increased levels of activation in the thalamus, while females featured weaker activation of hypothalamus and mammillary bodies and higher activation of caudate head and ventromedial pallidum (Poepl et al., 2016) (Fig. 1). These latter areas are involved in unconscious emotional attachment and pair bonding predominantly working in women during sexual stimulation. Moreover, the reduced activation of the hypothalamus in females supports the low self-reported concordance during sexual excitement and genital peripheral response. At the same time, the gain of thalamus activation in men is related to affective sexual involvement propensity (Poepl et al., 2016). Thus, gender-specific behavioural differences recognize a neurofunctional basis during the sexual arousal (Poepl et al., 2016).

After the cognitive phase, the following step encloses peripheral mechanisms, from changes in cardiovascular and respiratory functions until the genital response, showing obvious gender differences (Korff and Geer, 1983; Basson, 2002; Rupp and Wallen, 2008). In men, the penile blood flow increases, facilitating the erection, together with the pre-ejaculatory lubricant fluid production, the swelling and the testes ascent (Brunetti et al., 2008). In women, vaginal lubrication increases, cervix and uterus elevate to expand the vagina and prepare for sexual intercourse, together with changes in labia colour and size and the clitoris tumescence

and erection (Motofei, 2009). Although the cognitive activation pattern and these gender-related peripheral responses, the exact mechanism by which sexual desire and arousal are elicited is poorly documented.

Environmental factors may act simultaneously with gonadotropins and sex steroid hormones to regulate reproductive behaviours (Simonneaux and Bahougne, 2015). Cultural, psychological and relational factors could also influence sexual desire and impact on pituitary-gonadal axis (Corona et al., 2013b). Mutation of genes involved in the negative regulation of the steroidogenic function, such as the dosage-sensitive sex reversal, adrenal hypoplasia critical region located on chromosome X (*DAX-1*) (Lalli and Sassone-Corsi, 2003), could affect hormone production. Moreover, light and darkness synchronize the suprachiasmatic nucleus activity, controlling the frequency and amplitude of gonadotropin releasing hormone (GnRH) release from hypothalamic neurons, leading to the circadian rhythms of androgen actions (Model et al., 2015). Similarly, androgen and estrogen receptors expression in the suprachiasmatic nucleus is influenced by different circulating hormone levels in male and female (Bailey and Silver, 2014). Circadian rhythm is generated by the cyclic transcription of "clock" genes expressed in the central nervous system but also in peripheral organs, such as the ovary (Sellix, 2015). Phase shift of light/dark cycles and deletion of "clock" genes are associated with disruption of circadian rhythmicity and impairment of male and female reproductive function. As an example, knockout male mice for the "clock" gene *Aryl Hydrocarbon Receptor Nuclear Translocator Like (ARNTL)* demonstrated inability to mate with receptive females and exhibited low testosterone levels (Schoeller et al., 2016). Similar results were found in rats subjected to sleep deprivation (Alvarenga et al., 2015). In female mice, *ARNTL* deletion is associated with implantation failure (Ratajczak et al., 2009). Accordingly to what demonstrated by animal models, sleep disturbances are linked to increased risk of miscarriage and abnormal menstrual cycles in women (Labyak et al., 2002) and decreased sperm quality in men (Jensen et al., 2013), highlighting the fundamental role played by the circadian rhythm in human fertility. Indeed, light/dark cycles mediate the production of melatonin, which, in turn, regulates the expression of "clock" and steroidogenesis-related genes in peripheral tissues, such as Leydig cells. Pinealectomized rats displayed perturbation of "clock" genes expression, as well as *Stard1*, *Cyp11a1* and *Cyp17a1* gene expression, resulting in relatively high intracellular cAMP and serum testosterone levels. These parameters return within physiological range levels by melatonin replacement, restoring normal Leydig cell functions (Baburski et al., 2015).

2.2. Molecular basis of sexual desire

Sexual desire is a subjective expression of cerebral processes not completely understood, representing the prime mover of human reproduction to achieve copulation. However, other processes accompany sexual desire, such as motivation to have sexual activity and sexual arousal. All these actions are included in a complex cognitive framework, in which the stimulus entered in a feedback procedure involving experiential factors, affective state and social context. This psychological setting exhibits a molecular basis, in which hormones have a significant role acting on their receptors (Table 1) (Corona et al., 2016). In particular, androgen and estrogen receptors mediate the activation of intracellular signaling linked to somatic sexual stimuli, through autonomic afferent pathways activating the arousal cerebral centres (Motofei and Rowland, 2005). Taken together, these stimuli converge in the modulation of the levels of attention and sexual motivation (Rupp and Wallen, 2008).

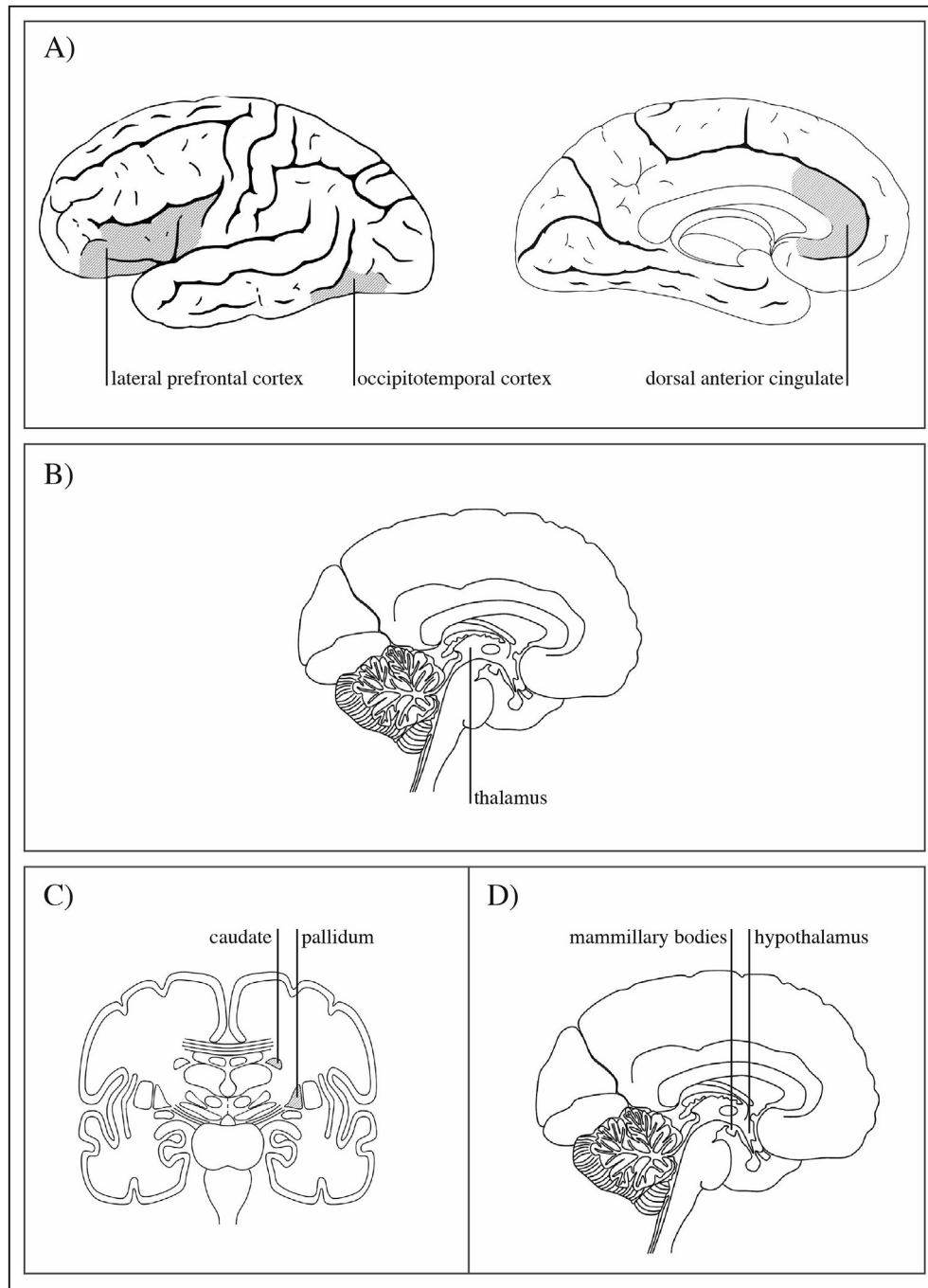


Fig. 1. Cerebral areas activated by sexual arousal. A) Cerebral activation in both sexes. B) Increased activated area in men. C) Increased activated areas in women. D) Reduced activated areas in women.

Pre-optic area and anterior hypothalamus display high aromatase levels and expression of estrogen receptors, suggesting that estradiol may be involved in the regulation of libido (Schulster et al., 2016). As a confirmation, exogenous administration of estradiol to hypogonadal men seems able to increase sexual desire (Wibowo et al., 2011). Interestingly, the role of estradiol is strictly related to testosterone levels in males. Indeed, in a hypogonadal man with aromatase deficiency, libido, sexual fantasies and sexual activity were recovered by combined estrogenic and androgenic therapy (Carani et al., 2005a), while the combined treatment by testosterone and aromatase inhibitors decreased estradiol levels

and impaired sexual drive (Schlegel, 2012; Finkelstein et al., 2013). In addition, estradiol is identified as a significant positive predictor of sexual interest both in fertile and postmenopausal women (Dennerstein et al., 2002; Roney and Simmons, 2013).

The relationship between sexual desire and other hormones, e.g. dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS), was also investigated, leading to confounding results. Small prospective studies did not find any correlation between adrenal hormones and sexual desire in patients with primary adrenal insufficiency treated by DHEAS (Granata et al., 2013), and in females (Bouchard et al., 2016). In addition, a meta-analysis of available double-blind

Table 1
Hormones impact on the sexual desire control.

	Involvement in male sexual desire	Involvement in female sexual desire	Evaluation in case of decreased sexual desire
Testosterone	High	Minor role	Strongly recommended in men
DHT	Minor role	Not demonstrated	Not recommended
Estrogens	Minor role and strictly related to testosterone levels	High	Not recommended
DHEA	Contradictory	Contradictory	Not recommended
DHEAS	Contradictory	Contradictory	Not recommended
Cortisol	Contradictory	Contradictory	Not recommended
Prolactin	High	High	Recommended both in males and females
Thyroid hormones	Contradictory	Contradictory	Not recommended
GH	Contradictory	Contradictory	Not recommended
IGF-1	Contradictory	Contradictory	Not recommended
Melanocortins	Contradictory	Contradictory	Not recommended

[DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; DHT = dihydrotestosterone; GH = Growth hormone; IGF-1 = Insulin-like growth factor-1].

randomized controlled trials documented that DHEA administration did not influence any component of sexual function in men (Corona et al., 2013a). On the contrary, uncontrolled studies indicated a positive effect of DHEA on sexual functions, especially libido (Bronner and Vodusek, 2011). Similarly, the role of cortisol is far to be elucidated, although a link between decreased libido and cortisol excess was found in patients affected by Cushing's syndrome (Valassi et al., 2011). However, cortisol could influence sexual desire both directly and, indirectly, through comorbidities associated with high cortisol serum levels (Corona et al., 2016).

Low levels of prolactin were related to metabolic, psychological, and sexual functioning, at least in terms of reduced orgasmic experiences, in middle-aged and elderly European men (Corona et al., 2014). However, how prolactin influences sexual desire is not completely understood and few hypotheses have been proposed so far. First, elevated prolactin serum levels increase the dopamine turnover in several brain areas, leading to suppression of GnRH and hypogonadism (Corona et al., 2016). Second, a direct effect of prolactin on sexual desire has been suggested, since its receptors are found in important areas for the control of sexual behaviour (Corona et al., 2016).

Thyroid hormones seem to influence sexual interest, indeed hypothyroidism is associated with a decreased libido, although the underlying mechanism remains unclear (Carani et al., 2005b). Hyper- and hypothyroidism are reversibly related to other sexual disorders, such as erectile dysfunction, confirming that thyroid hormones impact on sexual issues (Krassas et al., 2008). Finally, growth hormone, insulin-like growth factor-1 and melanocortins seem to be involved in the regulation of sexual desire, although no clear causalities have been identified so far (Shadiack et al., 2007; Hartman et al., 2013; Molitch, 2017).

The study of association between pheromones and libido showed interesting results. Pheromones are chemical messengers firstly detected in animals, where they contribute to attract the partner of the other sex (Zhang et al., 2008). The vomeronasal organ is deputed to process the signals mediated by these molecules through G protein-coupled receptors (GPCRs) expressed by sensory neurons, at least in mammals, but it was never clearly characterized in humans (Keverne, 1999). A large part of functional studies on the vomeronasal organ were performed in mouse models, where more than 250 putative pheromone receptors were identified, suggesting that the regulation of sex-specific chemosignals is complex and far to be elucidated (Isogai et al., 2011). On the other hand, the trait of pheromone detection has not been determinant for the evolutionary success of higher primates (*Catarrhini*), resulting in progressive decreasing of specific receptors and therefore, collapse of chemoreception during human evolution (Yoder and Larsen, 2014). Androstenol and androstenone are considered human male

pheromones, impacting on female sexual desire, menstrual cycle and ovulation. Similarly, copulin represents the female vaginal pheromone, influencing the male cognitive process of sexual arousal (Wyart et al., 2007). These putative human pheromones are progesterone derivatives and estrogen-like steroids linked to signals processed by sexual olfactory system through the medial pre-optic area and anterior hypothalamus, and by the common olfactory system, via amygdala, orbitofrontal and insular cortex (Motofei, 2009). Thus, the action of pheromones on these cerebral areas should be linked to sexual desire.

Finally, sexual functions are strictly connected with lysophospholipid signaling, which regulates the physiology of ovary and testis, acting via specific GPCRs (Ye, 2008). Lysosphingolipids like sphingosine 1-phosphate (S1P) have been proposed as strong regulators of vascular health (Yanagida et al., 2017) with a potential impact on vasculogenic sexual dysfunctions. Indeed, S1P-pathway is deeply involved in modulating endothelial functions, such as NO release, adhesion molecule expression, barrier effect (Yanagida et al., 2017), and protecting vascular bed from atherosclerotic degeneration, as demonstrated in animal models of disease (Poti et al., 2012, 2015). Regulation of vascular and non-vascular smooth muscle tone is a crucial event in the physiology of sex, indeed it is a known marker of both erectile and vaginal dysfunction in men and women, respectively (Baldassarre et al., 2015; Hackett et al., 2016). Relaxation of smooth muscle cells arises through the action of nitric oxide and other endogenously derived gases on cyclic guanosine monophosphate (cGMP)-pathway (Yetik-Anacak et al., 2015), representing a target of testosterone and estradiol to strengthen and maintain these functions (Comeglio et al., 2016).

3. Neurosteroids and their effect on sexual desire

The term neurosteroids refers to brain-synthesized steroids able to affect neuronal excitability (Paul et al., 1992; Reddy, 2010; Reddy et al., 2012). The main source of neurosteroids comes from the peripheral conversion of precursors, such as progesterone, deoxycorticosterone and testosterone. Consecutive reactions synthesize the final lipophilic product, which could rapidly cross the blood-brain barrier (Lambert et al., 2003; Reddy, 2010). The second source is represented by the central production, whereby the 5 α -reductase and 3 α -hydroxysteroid oxidoreductase (3 α -HSOR) enzymes produce neurosteroids directly in the neocortex, in the subcortical white matter and in the hippocampal tissues (Stoffel-Wagner et al., 2003) (Fig. 2). This process, called neurosteroidogenesis, takes place in cortex, hippocampus and amygdala, where synthetic enzymes are localized in glutamatergic principal neurons and not gamma-aminobutyric acid (GABA)-ergic inhibitory

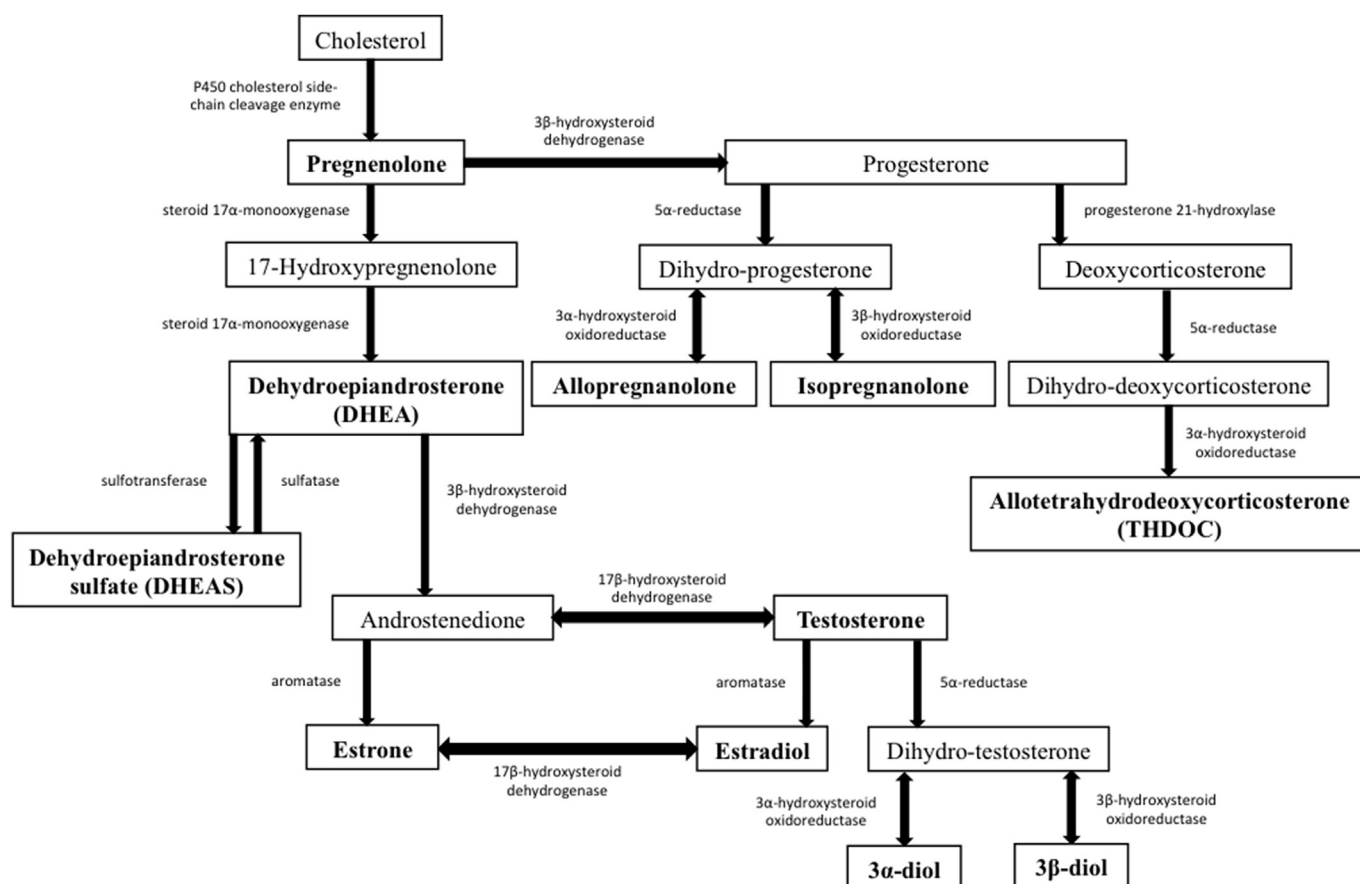


Fig. 2. Main biochemical pathways for neurosteroidogenesis in the brain.

neurons (Stoffel-Wagner et al., 2003). Here, neurosteroids perform an endogenous regulation of the brain excitability, through the direct interaction with membrane receptors and ion channels (Lambert et al., 2003; Reddy, 2010). Moreover, neurosteroids could act either through a classical genomic action or the metabolic inter-conversion to traditional steroids (Reddy, 2010). The role of neurosteroids was evaluated in animal models and in specific clinical settings, such as Alzheimer's disease or dementia (Chernoff et al., 2017), although results are often inconclusive.

Considering their biochemical structure, neurosteroids may be subdivided as pregnane neurosteroids, (allopregnanolone and allotetrahydrodeoxycorticosterone (THDOC)), androstane neurosteroids (androstenediol and etiocholanolone) and sulfated neurosteroids (pregnenolone sulfate and DHEAS) (Mellon and Griffin, 2002; Reddy, 2010). The GABA-A receptor is the major target of neurosteroids, which could be negatively or positively regulated depending on the chemical structure of the steroid molecule (Reddy, 2010). Allopregnanolone, THDOC and androstenediol are potent positive allosteric modulators of GABA-A receptors, whereas other neurosteroids modulate the N-methyl-D-aspartate (NMDA) type glutamate receptors (Reddy, 2010). In general, pregnane derivatives show sedative, anxiolytic and anticonvulsant actions, whereas sulfated neurosteroids have excitatory and anxiogenic effects (Reddy, 2010).

Dopamine neurotransmission plays an important role in sexual desire and arousal, through the aversive and reward learning processes (Brom et al., 2016). The demonstration of high prevalence of sexual dysfunctions in Parkinson's disease could represent an experimental model to confirm the role of dopamine in the control of sexual desire (Bhattacharyya and Rosa-Grilo, 2017).

However, there are no researches, involving humans, describing the possible action of neurosteroids to influence dopamine neurotransmission. In this context, the role of neurosteroids in sexual desire and sexual function was recently proposed in several studies describing a hypothetical "post-finasteride syndrome", characterized by persistent adverse effects in a subset of young men treated with finasteride for androgenic alopecia. These patients present a wide spectrum of signs and symptoms, such as erectile dysfunction, low libido, lack of orgasm and depression (Basaria et al., 2016; Melcangi et al., 2017). The correlation between depression and neuroactive steroid levels alteration is largely demonstrated in the literature (Uzunova et al., 2006; Zorumski et al., 2013). However, only the implication of neurosteroids in sexual desire could be proposed and no clear results have been achieved so far (Irwig, 2014; Traish et al., 2015).

4. Role of testosterone on sexual desire

Animal models suggested positive correlations between testosterone levels and sperm motility, and negative correlations with fat measurements and ejaculation latency time, revealing the hormone's impact on reproductive traits (Swelum et al., 2017). However, in humans, sex steroids also affect the first phase of sexual desire and the cognitive component of sexual arousal (Rupp and Wallen, 2008). Testosterone is a fundamental hormone for male sexuality, regulating both central arousal mechanisms and peripheral response (Bancroft, 2005; Wu et al., 2016), preparing the brain since early development to receive sexual stimuli during the adult life (Gagnidze and Pfaff, 2009). Although the relationship between testosterone and libido is largely demonstrated (Wu et al.,

2016), the exact mechanism by which it affects sexual desire is not clarified (Travison et al., 2006). Visual sexual stimuli are involved in sexual, emotional and motivational arousals in a testosterone-dependent pathway, modulating the activity of specific brain regions (Redoute et al., 2005). Together with testosterone, estradiol is involved in the regulation of male sexual desire, through a modulation of libido, erectile function, and spermatogenesis. Indeed, estrogen receptors are expressed in the brain, such as in the hypothalamic nucleus, representing an important region for the regulation of sexual behaviours (Mori et al., 2008), and in male sexual organs (Schulster et al., 2016), and the testosterone/estradiol ratio was proposed as a parameter reflecting the sexual status, although it is a debated issue (Castello-Porcar and Martinez-Jabaloyas, 2016).

4.1. Testosterone levels and sexual desire in eugonadal men

Erotic visual stimuli are largely used to evaluate sexual desire in experimental settings both in men and women. In men, visual sexual stimuli lead to a typical neural activation pattern at the right middle occipital and right inferior frontal gyrus, correlated with testosterone levels (Stoleru et al., 1999). However, opposite or not completely matching results were independently found (Travison et al., 2006; Gades et al., 2008), showing that the relationship between the cognitive processes related to sexual stimuli and testosterone levels remains challenging.

The role of testosterone in the regulation of sexual functions is documented in eugonadal men treated by GnRH antagonist, where decreased sexual interest and activity occurred according to the iatrogenic reduction of the hormone levels (Bagatell et al., 1994b). These results were confirmed using a different GnRH antagonist (Behre et al., 1995) and in androgen-deprived patients treated for prostate cancer (Strum and Scholz, 2016). On the other hand, in eugonadal men, the pharmacologically controlled variation of testosterone levels within the physiological range did neither increase the erectile function nor frequency of sexual activity, as measures of sexual desire (Anderson et al., 1992; Bagatell et al., 1994a; Yates et al., 1999), (Buena et al., 1993). Also the role of dihydrotestosterone administration has been recently evaluated in eugonadal men, suggesting that testosterone aromatization plays only a minimal role in the maintenance of sexual normal function (Sartorius et al., 2014).

All together, these data revealed that testosterone is involved in the modulation of sexual desire and relatively low hormone serum levels seem to be enough to achieve peripheral sexual arousability (Bancroft, 2005).

4.2. Low testosterone levels and sexual desire in hypogonadal men

The impact of testosterone on sexual interest at the brain level is reflected by different physiological responses to visual sexual stimuli between eugonadal and hypogonadal men (Park et al., 2001). In particular, specific brain regions, such as right orbito-frontal cortex, insula, *claustrum* and left inferior frontal gyrus, show different patterns of activation in an androgen-deficit condition compared to eugonadism (Redoute et al., 2005) and androgen replacement therapy restores the physiological brain response (Park et al., 2001; Mayor, 2016). Although the peripheral mechanism of penile erection is conserved in hypogonadal men viewing sexual stimuli (Kwan et al., 1983; Rupp and Wallen, 2007), nocturnal erections occurring during the rapid eye movement (REM) phase of sleep is impaired in hypogonadal men and restored by testosterone replacement (Bancroft, 2005). Nocturnal erections are a physiological process triggered by inactivation of the noradrenergic tone in the *locus coeruleus* at the brainstem (Bancroft,

2005). The expression of androgen receptors in the *locus coeruleus* supports that this central mechanism of unconscious sexual arousability is testosterone-dependent (Carani et al., 1995).

Sexual desire reduction is the most representative symptom caused by testosterone deficiency (Wu et al., 2010; Cunningham et al., 2015; Hsu et al., 2015; Isidori et al., 2015; Rochira et al., 2015), as demonstrated by testosterone withdrawal in hypogonadal men (Davidson et al., 1979; Luisi and Franchi, 1980; Skakkebaek et al., 1981; Salmimies et al., 1982; Kwan et al., 1983; O'Carroll et al., 1985). In particular, sexual interest declined within three to four weeks after androgen discontinuation and was re-established within two weeks of testosterone replacement (Bancroft, 2005). Moreover, testosterone supplementation is documented to improve sexual desire in older men with hypogonadism (Mayor, 2016; Snyder et al., 2016), as well as in young men with hypogonadism, obesity and obstructive sleep apneas (Melehan et al., 2016). Accordingly, androgen replacement therapy is associated with increased masturbation frequency, representing a sexual expression connected with sexual interest (Anderson et al., 1999; Bancroft, 2005). However, the effects of testosterone replacement therapy on the frequency of sexual intercourses are complex to evaluate, since depending on several variables including relationship characteristics (Anderson et al., 1999; Bancroft, 2005). A recent meta-analysis, including randomized clinical trials evaluating testosterone-treated men, demonstrated a significant improvement of libido and other aspects of sexual function (Corona et al., 2017). This improvement is evident when hypogonadism was present at baseline (Corona et al., 2017).

4.3. Androgen role on sexual desire in women

The relationship between testosterone and sexual arousal in women is still a matter of debate (Bancroft, 2005; Traish et al., 2007). Contrasting results might be due to the complexity of the endocrine system in females and the co-existence of psychological factors strictly involved in women sexuality. During the ovarian cycle, testosterone levels rise in the follicular phase achieving a maximum at the middle of the cycle. Differently from the male counterpart, sexual activity seems to be required to achieve the testosterone levels increase after visual sexual stimuli (Exton et al., 1999; van Anders and Dunn, 2009; Goldey and van Anders, 2011). The importance of the psychological component in women's sexuality is supported by the observation that anticipation of sexual activity seems to increase testosterone levels in women before intercourse but not before non-sexual activities (van Anders et al., 2007). A similar increase has been described in women the day before seeing their partners after a separation (Hamilton and Meston, 2010). Interestingly, even if hormonal contraceptive use results in a reduction of free serum testosterone by suppressing ovulation and increasing sex hormone-binding globulin levels (Swinkels et al., 1988; Bancroft et al., 1991; Coenen et al., 1996; Thorneycroft et al., 1999; Van Anders and Watson 2006, Greco et al., 2007; Edwards and O'Neal, 2009), no impairment of sexual interest is observed (Graham et al., 1995; Sanders et al., 2001; van Anders et al., 2007; Edwards and O'Neal, 2009). Similarly, no decrease in sexual interest was found in women with lower androgens levels induced by the anti-androgen cyproterone acetate (Appelt and Strauss, 1986). On the contrary, decreased testosterone and androstenedione levels were found in breast-feeding mothers complaining for low sexual desire (Bancroft et al., 1991). Interesting and informative results may be provided by women affected by polycystic ovary syndrome, characterized by hyperandrogenism, often featuring hirsutism, acne, metabolic dysfunction and other symptoms related to high androgen levels (Azziz et al., 2016). In these women, clinical signs of androgens sensitivity, rather than

serum testosterone levels *per se*, predicted the measure of specific aspects of sexual desire, such as mating selection (Bellini et al., 2013). Therefore, testosterone levels may not explain the full physiological mechanism regulating women's sexuality.

Several studies reported a decline of sexual interest in both natural and surgical menopause, when hormonal levels decline, although a clear relationship between testosterone and sexual arousal was not found (Cawood and Bancroft, 1996; Kirchengast et al., 1996; Dennerstein et al., 2003; Bancroft, 2005). At the same time, the testosterone role on women sexuality was suggested by a recent meta-analysis, evaluating 3035 post-menopausal women affected by hypoactive sexual desire disorder. This pathology consists in deficiency or absence of interest for sexual activity, linked to distress or interpersonal difficulty. Patients randomized to transdermal testosterone treatment displayed more satisfying sexual episodes and orgasms, as well as increased sexual activity, compared to the placebo group (Achilli et al., 2017), in spite of increased risk of hyperandrogenism-related side effects, such as acne. In conclusion, testosterone plays a significant role in the regulation of some aspects of female sexuality, although the real extent of this relationship could be masked by affective and psychological mechanisms markedly present in women (Bancroft, 2005).

5. Testosterone action

At the molecular level, testosterone and its agonist 5 α -dihydrotestosterone act through the androgen receptor (AR), a nuclear receptor located in the cytoplasm and translocating to the nucleus upon ligand binding (Pihlajamäe et al., 2015). AR is expressed in several androgen-regulated tissues in both sexes, as well as in some cancer cells, modulating reproductive and aggressive behaviours, which are counterbalanced by adrenal signals (Cunningham et al., 2012). However, rapid androgen-dependent signaling may occur via a relatively new GPCR mediating non-genomic effects (Pi et al., 2010) and endocrine functions (Clemmensen et al., 2014).

5.1. Genomic effect

The gene encoding AR is located on the X chromosome and is expressed in several tissues. Upon ligand binding, AR translocates to the nucleus where it recognizes androgen response elements (AREs) and acts as a transcription factor, regulating cell metabolism and proliferation. However, the final, physiological effect of androgens depends on the type of target cells (Castoria et al., 2017).

The evaluation of molecular aspects at the brain level generally requires histological dissections, thus it is not feasible in living human. Therefore, even if in a relatively small number, information on testosterone action are provided by studies in animal models, where it was demonstrated that the cognitive functions are strictly related to synaptic plasticity, which is regulated by testosterone. In a mouse model of Alzheimer's disease, testosterone acts through AR expressed in the hippocampal CA1 region increasing dendritic spine density via cyclic adenosine monophosphate (cAMP)/cAMP responsive element-binding protein (CREB) pathway (Jia et al., 2016). The effect is depleted by treatment using the AR antagonist flutamide, resulting in decreased levels of CREB phosphorylation and brain derived neurotrophic factor, suggesting a positive testosterone impact on synaptic plasticity and cognitive functions fundamental for reproduction.

Testosterone modulates sexual functions mainly acting on dopaminergic neurotransmitters (Jordan et al., 2011). Indeed, mouse models demonstrated co-expression of AR and genes involved in dopaminergic transmission in specific cerebral areas, indicating the presence of steroid-regulated pathways in the brain (Mahfouz et al., 2016). In the mouse suprachiasmatic nucleus,

androgens are required for the light-induced *mPer1* clock gene expression and downstream neuronal protein pattern. This is impaired in gonadectomized mice and restored upon dihydrotestosterone administration (Karatsoreos et al., 2011). Thus, androgens may be involved in the regulation of behavioural responses to light/dark cycles impacting on reproduction. Social, emotional and reproductive behaviours may be modulated by testosterone, acting at the medial nucleus of the amygdala, inducing *Kiss1* gene expression, encoding the kisspeptin protein (Kim et al., 2011). In the amygdala of gonadectomized rodents, *Kiss1* expression levels decreased in both sexes, and replacement therapy with testosterone or estradiol restores its physiological expression. Since kisspeptin stimulates the release of GnRH and pituitary gonadotropins (Smith et al., 2005; Pasquier et al., 2014), an androgen-dependent regulation of sexual behaviours and peripheral responses is suggested. On the other hand, sex-specific and hormone-dependent behaviours, such as territorial aggression and sexual display, are well known in several species, revealing further roles of androgens in the brain. Interestingly, the regulation of sexual and social behaviours might be dependent on the sensitivity of brain target tissues to steroids, rather than serum hormone levels. A study evaluating sex-role reversal in birds (*Centropus grillii*), where females are more aggressive and competitive for resources than males, demonstrated that the expression pattern of androgen receptor in brain nuclei regulating reproductive and aggressive behaviours is higher in females than in individuals of the opposite sex, reflecting the agonistic role in their social environment (Voigt and Goymann, 2007).

5.2. Different AR response due to CAG and GGN repeats

In humans, sensitivity to testosterone may be modulated by the AR genotype. The length of cytosine-adenine-guanine (CAG) or guanine-guanine-N (GGN; where 'N' indicates "any nucleotide") repeats within the exon 1 of the AR gene is linked to the activity of the receptor and to androgen sensitivity (La Spada et al., 1991). *In vitro* experiments revealed an inverse correlation between the number of repeats and the receptor sensitivity, which is higher for receptors carrying lower number of repeats (Chamberlain et al., 1994). However, these polymorphic variations are well conserved among primates (Hong et al., 2006), suggesting that they may confer a variability of reproductive trait useful for the establishment of sexual behaviours and complex social dynamics between the individuals of their societies. In fact, AR genotype impacts on reproductive traits and is linked to specific phenotypes, such as polycystic ovary syndrome in women (Shah et al., 2008) and androgen levels in men (Bogaert et al., 2009). It is reflected by higher anaerobic sport performance of boys carrying short AR CAG repeat polymorphism than those featuring relatively high number of repeats (Rodríguez-García et al., 2017). Highly androgenic men, presenting elevated testosterone levels and shorter CAG number, display relatively elevated likelihood of relationship instability and lower involvement with childcare as fathers, than men featuring low androgenicity (Gettler et al., 2017). Several studies suggested a possible role of CAG repeats on the clinical phenotype relevant for the management of hypogonadal men and women (Francomano et al., 2013). However, the role of pharmacogenomic investigations to select patients responding to androgen administration is still debated (Francomano et al., 2013).

The relationship between AR genotype and sexual desire is difficult to establish (Elaut et al., 2010). High sensitivity to testosterone due to long CAG repeats may be linked to self-esteem, aggressiveness and impulsivity in men (Vermeersch et al., 2010; Aluja et al., 2011; Konno et al., 2011) and it is reflected in the psychopathology of patients affected by Klinefelter syndrome, which

depends on parent-of-origin of the extra X chromosome (Bruining et al., 2010). This is indicative of how low testosterone levels, in men, are linked with higher propensity to be partners and fathers, while high testosterone levels support competitive behaviours for resources and mating (Simmons and Roney, 2011), as two different strategies to maximize the reproductive success of male individuals.

5.3. Non-genomic effect

Testosterone interacts with the so-called GPRC6A, a widely-expressed GPCR, regulating endocrine functions (Pi et al., 2017). GPRC6A may be involved in metabolic and bone functions via a non-genomic pathway, as shown by knockout mice developing metabolic syndrome, insulin resistance, osteopenia and unbalancing of serum steroid hormone and gonadotropin levels. On the contrary, the overexpression of this receptor is linked to prostate cancer. Indeed, GPRC6A mediates the activation of protein kinase A/extracellular-regulated regulated kinase (PKA/ERK1/2)- and protein kinase B (AKT)-pathways, resulting in proliferative and anti-apoptotic events (Fujiwara et al., 2014). The receptor is highly expressed in the brain, where it might be involved in the regulation of exercise, food intake and energy metabolism (Clemmensen et al., 2013). GPRC6A has been recently removed from the orphan receptors' list, but the full understanding of its functions and its impact on sexual desire are widely unknown.

6. Conclusion

Sexual arousal and desire are physiological and motivational issues important for reproduction. Neurosteroids, pheromones, lysophingolipids and other molecules contribute at establishing the physiological sexual response in both sexes. In humans, sexual behaviours may be distinct from reproductive behaviours and rely mainly on the action of testosterone on membrane and nuclear receptor localized in the brain and peripheral tissues. Sexual desire is a central event for reproduction and is dependent on the action of testosterone at the brain level in both men and women. The sexual stimulus is cognitively recognized and activates autonomic cerebral centres by acting on somatic afferent pathways, leading to increased neural activity in specific cortical areas. The AR exists in various genetic variants providing different cell response to the hormone and a wide range of phenotypes featuring own sexual behaviours. These phenotypes may be linked to specific reproductive strategies relying on propensity to kin care or competition for mating.

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