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Review

Molecular basis of androgen action on human sexual desire

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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.

Contents

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 (Poeppl 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 (Poeppl 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 (Poeppl 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 (Poeppl et al., 2016). Thus, gender-specific behavioural differences recognize a neurofunctional basis during the sexual arousal (Poeppl 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).