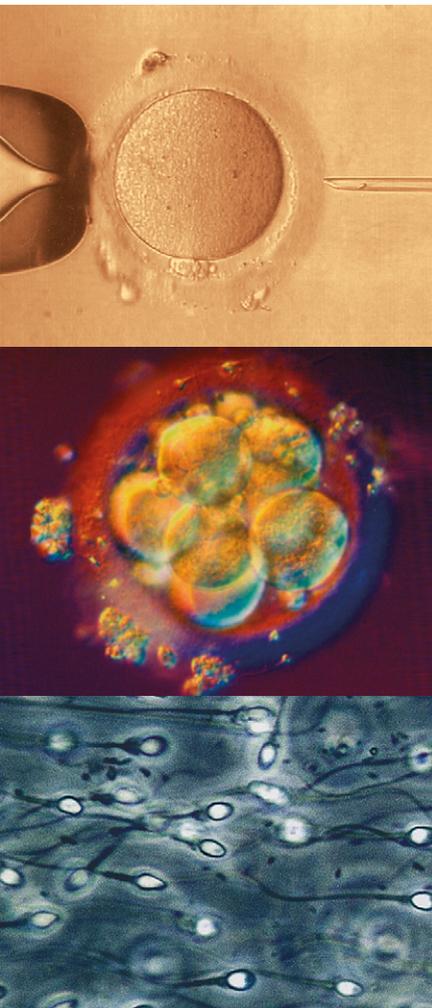


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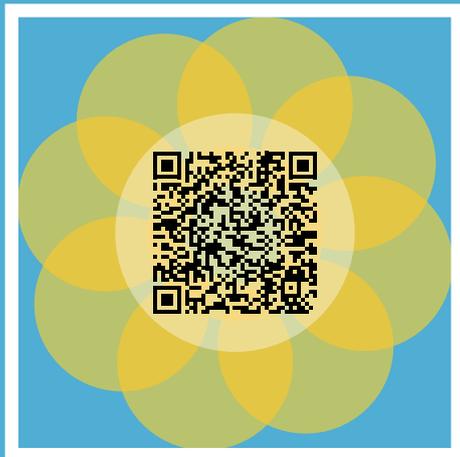
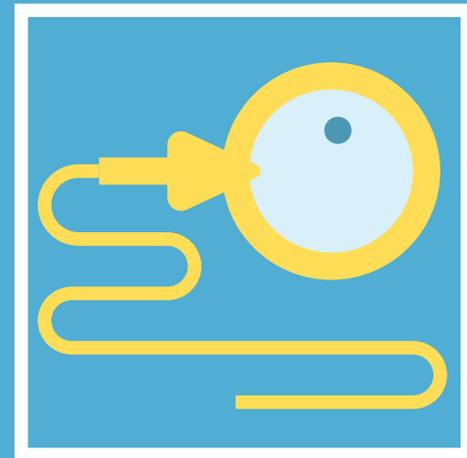
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**BACK TO THE FUTURE**

# Pathophysiology of Erectile Dysfunction – an Organisation/Activation Concept

K. Kula, J. Slowikowska-Hilczer, W. Kula

*Erection supposes a process regulated by hormonal and neuro-vascular mechanisms on both cerebral and peripheral levels. The current understanding of erectile function and dysfunction (ED) does not provide, however, a coherent model that accounts for the integration of sex hormones action and neuro-vascular mechanisms. Herein we suggest a model that involves organising and activating roles of sex steroids and neuro-vascular mechanisms in the regulation of erectile response. The organising role of hormones initiates during fetal life when androgens evoke both organogenesis of a penis and morphogenesis of a male type structure of sexually dimorphic brain regions (SDBR) responsible for male sexual behavior. Due to androgen-stimulation, penile growth proceeds in early childhood, is accelerated at puberty and ceases thereafter despite high androgen levels. Similarly, masculinisation of SDBR may extend to the adulthood but these structures may not be susceptible to hormonal manipulations thereafter. The activating component of erection appears also on both cerebral and peripheral levels. Since puberty male type of androgen/estrogen balance may simultaneously activate cerebral sympathetic tone responsible for sexual drive (libido) and parasympathetic tone responsible for erectile response on spinal cord level. On periphery the neuro-vascular activation of erection is present since fetal life and not dependent on libido. ED, the inability to achieve and maintain the erection to penetrate the vagina, may be of developmental origin as a primary failure or may derive from organic or psychogenic diseases as secondary failure. As primary, ED may result from the lack or insufficient organising role of sex hormones on penile and behavioral levels, androgen-treatment will be necessary. In turn, secondary ED is more frequent, may result predominantly from the disturbances in the neuro-vascular erection activating mechanisms, and is less responsive to androgen-treatment. **J Reproduktionsmed Endokrinol 2005; 2 (4): 246–50.***

**Key words:** sex hormones, penile organogenesis, erection, male sexual behavior, libido, erectile dysfunction

Penile erection is a sexually active state of a penis which becomes enlarged, rigid, and capable of penetrating the vagina. Its biological role is sperm deposition in the vagina to achieve fertilisation and sexual relations. Erection occurs, when blood flow to the penis exceeds blood flow out. The process is initiated by recruitment of afferent signals created by visual, acoustic, tactile, and imaginary erotic stimuli. These stimuli are processed in the limbic system to generate neuronal signals, which are carried through thalamospinal tracts to the penis. At penile level erection is determined by smooth muscle cells reactivity to neuronal signals, involving three haemodynamic components: (1) relaxation of cavernosal smooth muscles leading to intracavernosal reduction of resistance, (2) increased arterial inflow into the sinuses of the corpora cavernosa, and (3) restriction of venous outflow (veno-occlusion) by compression of intracavernosal and subtunical venous plexus against tunica albuginea of the corpora cavernosa [1]. Erection appears also as non-erotic, autonomous, mostly nocturnal.

Erection is regulated by hormonal and neuro-vascular mechanisms on both cerebral and peripheral levels. The current understanding of erectile function and dysfunction does not provide, however, a coherent model that accounts for the integration of sex hormones action and the mechanisms that are directly responsible for erection on neuro-vascular level. Herein we suggest a model that involves the organising and activating role of sex hormones, androgens and estrogens, assuring erection that may be disintegrated in erectile dysfunction (ED). The delineation of organising and activating components in erectile response is important to understand the mechanisms underlying ED. This dual concept could help to solve common disagreements between those who postulate only the endocrine aspects of ED and those neglecting them.

## Organising Role of Sex Hormones

### Penile Organogenesis and Growth

Penile development depends on two mechanisms: organogenesis and growth. While organogenesis occurs in the fetal life, penile growth proceeds during fetal life, early childhood and is accelerated at puberty. Testosterone and its more potent metabolite dihydrotestosterone (DHT) are essential for both organogenesis and growth of a penis. Hypospadias is the retardation of penile organogenesis and results from abnormal penoscrotal closure at the time of sex differentiation in the male embryo. The etiology is related to insufficient amount and action of androgens due to testicular dysgenesis, abnormalities of androgen receptor, deficiency of 5- $\alpha$ -reductase activity i. e. lack of DHT formation [2, 3]. Incomplete masculinisation of external genitalia occurs during the sensitive window between the 7<sup>th</sup> and the 12<sup>th</sup> week of gestation and cannot be overcome by even high doses of androgens at later stages of development. It indicates that androgen target tissues must undergo definitive and irreversible alterations during ontogenic process of penile organogenesis. Alternatively, masculinisation of male external genitalia may cease due to inhibitory action of estrogens in the human male fetus [4]. Estrogens have been demonstrated to act indirectly, reducing fetal androgens production by limiting growth of Leydig cells and inhibiting activity of steroidogenic enzymes involved in testosterone synthesis [5]. Recently, the presence of functional estrogen receptor has been demonstrated in differentiating male external genitalia, what indicates a possible novel role of estrogen in the regulation of the development of these sex structures [4, 6]. Estrogen inhibits directly proliferation of fetal smooth muscle cells of the penis, while androgen stimulates their proliferation, suggesting that the development of male urogenital structures results from a complex balance between androgen and estrogen.

The Penis grows until the age of five, then a latency period follows until puberty. During sexual maturation the penis size increases relatively to the rising testosterone secretion. However, penile growth ceases at the completion of puberty despite continued high levels of testoster-

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one. The exact mechanism of penile growth cessation remains unknown but it is not due to the down-regulation of androgen receptor [7]. Administration of testosterone does not stimulate penis growth in eugonadal adult men [8, 9] but it does in hypogonadism. The extended susceptibility to the androgen organising influence in hypogonadism beyond the time of the expected puberty can be explained by unsaturation of androgen receptor. While in eugonadal men testosterone within the normal range saturates androgen receptors and androgen effects reach a plateau [10], in hypogonadism androgen effects increase linearly with the logarithm of blood testosterone levels, acquiring finally a plateau [11]. According to the hypothesis of Hiort and Zitzmann [12], in hypogonadism androgen effects are strongly dependent on androgen blood levels as testosterone binds to androgen receptors and increases androgen effects until saturation is reached. However, even in mature animals deprivation of androgen results in a decrease in cavernosal smooth muscle content, their apoptosis, and atrophy [13], as well as in disturbances of erection by reduction of veno-occlusion [14], indicating that in androgen-deficient adult male the organising role of androgen is active.

### **Masculinisation of the Human Brain**

The male type structures of sexually dimorphic brain regions (SDBR) are a median preoptic area of the anterior hypothalamus (MPOA) and a central subdivision of the bed nucleus of the stria terminalis (BSTc). They are parts of the limbic system, participating in gonadotropin releasing hormone (GnRH) biosynthesis as well as in the creation of male gender behavior, sexual orientation, and erectile function [15, 16]. Tactile or psychic stimuli caused by erotic activity are processed to the MPOA and the nucleus paraventricularis to generate neuronal signals, which are carried through thalamospinal tracts to assure erection.

It has become recently evident that endogenous hormones more than socio-environmental factors influence gender differences. Experimental studies on animals revealed that transient action of sex steroids during the perinatal period of life is crucial for the development of male sexual behavior in adulthood [17]. In rodents, primates and probably in men masculinisation of SDBR is created during fetal and early postnatal life with the involvement of androgens and their local metabolism to estrogens [18, 19]. BSTc in men has 1.7 times more neurons than in women but only in adulthood [20], what indicates that this difference is acquired during development. Male patients with disturbances of sexual differentiation of external genitalia due to the lack of testosterone transformation into DHT or due to the inborn excess of androgens in women (congenital adrenal hyperplasia) have the affections in the formation of gender. In these individuals the legal sex established according to somatic sex and/or genetic sex at birth may be incompatible with their actual gender identity and role [21, 22]. Inversion of the male type structure of BSTc into female type is observed in men with female gender identity (male-to-female transsexualism) [23]. Although direct evidence that this inversion is dependent on changes in prenatal exposure to sex hormones is still not possible, there are some indirect evidences. Namely, adult male-to-female transsexuals reveal increased frequency and amplitude of LH secretory pulses despite normal secretion of testosterone [24], as well as increased basal and GnRH-stimulated blood levels of LH associated with normal serum levels of

testosterone [25, 26]. These changes are indicative for an incomplete differentiation and function of the male hypothalamus [27]. It has been shown that gender identity in transsexuals does not change under the influence of sex hormone administration [28]. It was found also that human BSTc is not susceptible to hormonal manipulations in adulthood [29]. These data support the concept of the developmentally-limited organising role of sex steroids in the creation of brain sex differences.

Prepubertal castration in boys prevents the development of libido and erotic-induced erections. However, although in adult men castration produces loss of libido, some of them retain erectile capabilities in response to erotic stimuli. In fact, while after treatment with GnRH-antagonist in normal men testosterone secretion is reduced to postcastration levels, the substitution with testosterone (that increased blood level of testosterone up to 400 ng/dl), did not produce an increase in libido and sexual activity [11]. These indications reduced sensitivity to androgen deprivation in adult men and reduced capabilities of androgens to stimulate libido after puberty. The lack of increased libido and erectile response during testosterone administration in adult eugonadal men [8, 9] may also be due to developmentally-limited organising role of androgen to create libido.

Although our knowledge on the molecular aspects of the differentiation of the male brain and genitalia is still limited, the role of sex hormones in penile organogenesis and growth as well as in the differentiation of the male brain can be considered as to be an organising one as they are the prerequisite for adult male sexual response and are developmentally limited.

## **Activating Role of Sex Hormones**

### **Supra- and Intrapenile Activation of Erection**

Neuronal signals from SDBR are coordinated in midbrain to generate signals which are carried through thalamospinal tracts. They leave the spinal cord through nerve roots at Th11–L2 for sympathetic travelling through hypogastric nerves (inhibitory), as well as via S2–S4 for parasympathetic nerves (stimulatory) and travel jointly through the pelvic plexus and the cavernous nerve to the penis [30].

Since fetal life the neuro-vascular mechanisms activate erection, which is in childhood not dependent on libido (non-erotic erection) [31–33]. Efferent erection-activating nerves are parasympathetic, non-cholinergic, with nitric oxide (NO) as final neurotransmitter. NO binds to smooth muscle cells of penile arteries and corpora cavernosa and increases the intracellular amount of cGMP and cAMP, followed by a decrease in intracellular calcium, smooth muscle relaxation, and finally erection. Penile neuronal, endothelial, and cavernosal NO synthases are stimulated by insulin, angiogenic cytokines, vasoactive intestinal peptide (VIP), and testosterone [34]. Cyclic nucleotides are broken down by the enzymes phosphodiesterases (PDE). Detumescence can be the result of adrenergic discharge during ejaculation, breakdown of cyclic nucleotides by PDE and cessation of erectile neurotransmitters release. Recently, oxytocin is postulated to induce contractility of smooth muscle of corpora cavernosa and thus is responsible for penile flaccidity. In a rabbit model of hypogonadism oxytocin responsiveness was strongly reduced and was completely restored by

estradiol. Corpora cavernosa express estrogen receptor  $\alpha$  and estrogen receptor  $\beta$ , as well as aromatase. It is hypothesised that estrogen may participate in inducing post-organic penile flaccidity by regulation of corpora cavernosa responsiveness to oxytocin [35].

In men revealing a decline in serum bioavailable testosterone, the treatment with PDE5 inhibitors was not effective but became effective to facilitate erection after co-administration of testosterone [36]. It has been recently found that testosterone supplementation completely restored PDE5 expression, erectile response to electrostimulation, and responsiveness to PDE5 inhibitor, which occurred after surgical castration [37]. Decreased sexual activity by itself results in decreased secretion of testosterone that recovers with the resumption of coital activity [38]. Does this indicate that men with sexual quiescence may develop a kind of "relative" or transient hypogonadism, leading to the diminished activation of erectile mechanisms?

### **Activation of Libido**

The activating component of erection involves central dopaminergic and adrenergic receptors in MPOA [39].  $\alpha$ -MSH, ACTH, VIP, pro-opiomelanocortin (POMC) derivatives and oxytocin are involved [40]. Beside these specific signals sexual arousal and erectile response involve concomitant activation of two antagonistic autonomic systems: sympathetic and parasympathetic, each operating on different neuronal levels. The sympathetic autonomic system plays a role in cerebral sexual arousal [41], while parasympathetic mediates sexual erectile response on spinal cord level [42]. According to the hypothesis of Motofei and Rowland [43], the gonadal hormones androgen and estrogen activate both systems, transforming pre-pubertal (non-erotic) genital stimulation with primitive erections on the spinal cord level into post-pubertal, mature erogenisation of sexual arousal on the cerebral level.

Recent research elucidated the mechanisms of sex hormones action in the male sexual behavior. Animal and human models of congenital estrogen deficiency provide evidence on the role of estrogen receptor  $\alpha$  in the male copulatory behavior [44]. A study of a man with aromatase deficiency did not reveal any abnormalities in gender identity and sexual orientation but did negatively influence libido. Sexual investigation of a hypogonadic man with aromatase deficiency, before and during testosterone or estradiol treatments, or during both medications simultaneously, showed that a great increase in libido, the frequency of masturbation and sexual fantasies were induced when the associated treatment was applied and both testosterone and estradiol reached the normal ranges [45]. This indicates that estrogens only in co-operation with androgens could play a role in the activation of the male sexual response. So, libido and male sexual activity seem to be activated post-pubertally by both gonadal hormones androgens and estrogens.

## **Erectile Dysfunction**

ED is the inability to achieve and maintain the erection to penetrate the vagina. Causes of ED may be primary of developmental origin and secondary deriving from organic or psychogenic diseases. In primary ED the distur-

bances of sex hormone organising roles are probably crucial while in secondary ED the failures in the activating mechanisms of erection may prevail.

Disturbances in neuro-vascular activation are probably the most frequent causative factors of organic ED. ED coexists with diabetes mellitus (35–70 % of patients with ED), vascular insufficiency (64 % of patients), and rarely with hyperprolactinaemia (< 2 % of patients) [46]. In diabetes ED results from failure in activation of penile neuronal, endothelial, and cavernosal NO synthases. In addition, smooth muscle cell damage and defective vasodilatation are caused by auto-oxidation of cell membrane and peroxidation of unsaturated fatty acids [47]. ED was found in patients with arterial (19 %), veno-occlusive (52 %), and mixed (29 %) variants of vascular insufficiency [48]. The incidence of cardiovascular disease closely correlates with the prevalence of ED. ED is also thought to be an early signal of impending cardiovascular disease [49]. In arteriosclerosis ED is exaggerated by induction of fibrogenic cytokine, transforming growth factor-beta 1 (TGF $\beta$ -1) and its type II receptor under continuous ischaemic conditions, resulting in fibrosis of the penis [50]. It seems that ED of ageing male results also from arteriosclerosis-dependent cavernosal fibrosis and veno-occlusive dysfunction, rather than from decreased testosterone levels [51]. Sometimes, lower results of a single serum total testosterone determination (according to local norms) in otherwise healthy men are considered meaningful to diagnose "andropause". It disregards that individual changes in testosterone secretion throughout life are not known and that the available cohort longitudinal studies reveal only a slight, age-dependent decrease in testosterone secretion (–0.8 %/yr) between the 40<sup>th</sup> and 70<sup>th</sup> year of life [52]. In other cohort studies, no such decline was noticeable [53]. Nevertheless, a recent study on the factors affecting the variability in individual circulating levels of sex steroids and their precursors identified age as the most important factor, followed by body mass index (BMI), race, and lifestyle factors [54]. Among men with ED, deficiency of testosterone is estimated to be between 1.7 % and 18.7 % of patients. This wide range could be explained by uneven clinical material, different definitions of low testosterone levels, or single versus repeated testosterone determinations [55]. Disregarding these discrepancies, this figure suggests that decreased secretion of testosterone may not be essentially responsible for ED in the aging male. ED may coexist also with systemic, neurogenic, and penile diseases and may occur as iatrogenic (i. e. post-surgical). Many of ED patients develop secondary psychogenic alterations to the organic disorders, so the etiology is frequently mixed.

Psychogenic ED (about 35 % of ED patients) may be diagnosed via exclusion of organic type by measuring erectile response to intracavernosal injection of vasoactive substances (normal response in psychogenic ED) [48]. It includes depression and severe or chronic stress (life problems, overwork, fear of failure in sexual relationships, partner problem). Earlier traumatic experiences and upbringing are also important. Negative interrelations between the hypothalamo-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis were found. In stressed men blood testosterone level is decreased. This is explained by the fact that stress and depression activate the hypothalamo-pituitary-adrenal axis, what diminishes the activity of hypothalamic-pituitary-gonadal

axis. Hence, secretion of testosterone decreases due to reduction in LH pulse amplitude and frequency [56]. Under animal experimental conditions, after an initial large response to stress, the prolonged stimulation leads to a gradually reducing plasma corticosteroid concentration. This has been interpreted as a reduction in perceived stress signal severity or habituation to the negative stimulus, so the animal deemed less stressed. However, this reduction may be due to the intrinsic control mechanisms designed to prevent prolonged increases in corticosteroid concentrations. The stress signal at higher brain levels may still be present and the animal may still be experiencing the stimulus as aversive [57]. It is speculated, that in the etiology of depression and chronic stress the relative levels of sex hormones play a more important role than their absolute levels [56].

This bulk of evidences suggests that unavailability of sex hormones in the developmental period of life may cause a primary lack of erection but is less frequent although highly effective to the treatment with androgens. In turn, ED appearing as a disturbance secondary to different generalised diseases like arteriosclerosis, diabetes, or psychogenic disturbances is more frequent and less responsive to the treatment with androgens. Despite different pathogenesis, secondary ED may involve impaired activating component of erection appearing as an end organ-unresponsiveness to supra- or intrapenile neuronal stimuli. Insufficient action of sex steroids despite their normal blood levels may participate only partially to the pathogenesis of secondary ED.

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