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Psychological stress and the function of male gonads

Stres psychiczny a czynność gonad męskich

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Abstract
Stress is generally a natural phenomenon that affects behaviour, physiological processes, and neuroendocrine, neurochemical, neurological and immune responses. Many somatic and mental disorders are thought to result from chronic stress. Stress-induced gonadal dysfunction is not restricted to humans, but is observed in all higher animals. Stress-induced gonadal dysfunction comprises disturbances of the hypothalamic-pituitary-gonadal axis and of spermatogenesis. Various stressors induce changes in the secretion of neurotransmitters and hormones, such as CRH, ADH, beta-endorphins, somatostatin, VIP, PRL, GH, TSH, dopamine, serotonin, neuropeptide Y, melatonin, ACTH, glucocorticosteroids, catecholamines and androgens. In acute stress, testicular function is principally modified by cytokines and fluctuating concentrations of gonadotropins, while in chronic stress, hypogonadotropic hypogonadism and disruption of spermatogenesis of varying severity, including spermatogenetic arrest, are observed. In spite of the decades-long interest in the relationships between psychological stress and the function of male gonads, many questions in this area remain unanswered. **(Pol J Endocrinol 2012; 63 (1): 44–49)**

Key words: *psychological stress, testis, gonadotropins, androgens, semen*

Streszczenie
Stres jest generalnie zjawiskiem naturalnym, wpływającym na zachowanie, procesy fizjologiczne, reakcje neuroendokrynne, neurochemiczne, neurologiczne i immunologiczne. Jednocześnie uważa się, że wiele schorzeń somatycznych i psychicznych jest efektem przewlekłego stresu. Wywołana stresem dysfunkcja gonad dotyczy nie tylko ludzi, ale jest obserwowana u wszystkich zwierząt wyższych. Obejmuje ona zaburzenia czynności osi podwzgórzowo-przysadkowo-gonadalnej i spermatogenezy. Pod wpływem różnorodnych stresorów dochodzi do zmian stężeń neurotransmiterów i hormonów, które działają obwodowo m.in.: CRH, ADH, beta-endorfin, somatostatyny, VIP, PRL, GH, TSH, dopaminy, serotoniny, neuropeptydu Y, melatoniny, ACTH, glikokortykosteroidów, katecholamin, androgenów. W stresie ostrym czynność jąder jest modyfikowana głównie przez cytokiny i wahania stężeń gonadotropin. W stresie przewlekłym często obserwuje się hipogonadyzm hipogonadotropowy i różnego stopnia zaburzenia funkcji plemnikotwórczej, aż do zatrzymania spermatogenezy włącznie. Duże zainteresowanie relacjami między stresem psychologicznym a czynnością gonad utrzymuje się od kilkudziesięciu lat. Wiele kwestii w tej sferze wciąż pozostaje jednak niewyjaśnionych. **(Endokrynol Pol 2012; 63 (1): 44–49)**

Słowa kluczowe: *stres psychologiczny, jądro, gonadotropiny, androgeny, nasienie*

Definition of stress

Attempts to define stress have been made in the medical literature for more than 70 years [1]. Defining stress as a non-specific response of the body to various stress stimuli (stressors) emphasises the fact that stereotypical responses of the body are typical in their manifestation, although their cause is non-specific. At the same time, stress of the same strength evoked by the same stressor may trigger different effects in different people [2].

The general adaptation syndrome (GAS) may be divided into three principal stages:
— Alarm;
— Resistance;
— Exhaustion.

Stress is generally a natural phenomenon necessary for mobilisation of the body in a state of danger. Acute stress develops in everyday situations, manifests itself by adrenergic activation and is not pathogenetic. In chronic stress, on the other hand, the excessive intensity or number of stressors or a persistent exposure to them may lead to responses that are disproportionate to the actual danger. Many somatic and mental disorders are thought to result from chronic stress [3].

Epidemiology of stress

Estimated data originating from geographically distant places in the world suggest a relatively large exposure of women and men to psychological stress (Table I).

While comparing the results, it should be borne in mind that there is no single universally accepted standard for the evaluation of stress. Some of the instruments used in population studies include the 12-item General

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Table I. *Worldwide prevalence of psychological stress*
Tabela I. *Rozpowszechnienie stresu psychologicznego na świecie*

Study	Country	n	Age	Psychological stress (% of the study population)
Sparrenberger et al. 2003 [43]	Brazil	3,942	> 20	14–32
Kikkinen et al. 2007 [44]	Australia	1,563	25–74	31
Tabak et al. 2008 [45]	Poland	1,379	18 (mean)	> 40
Caron et al. 2010 [12]	Canada	36,984	> 15	19
Hamer et al. 2010 [46]	United Kingdom/Australia	11,546	> 18	13

Health Questionnaire (GHQ-12) [4], the K-6 and K-10 scales [5], the WHO Well-being Index and the WHO World Mental Health Composite International Diagnostic Interview (WMH-CIDI). The tools/questionnaires differ in terms of sensitivity and specificity [5].

Pathophysiology of stress

Stress affects behaviour, physiological processes, neuroendocrine, neurochemical, neurological and immune responses. The typical physiological manifestations of stress include disorders of sleep and biological rhythms, suppression of the appetite centre, dysregulation of gastrointestinal peristalsis, changes in the perfusion of internal organs, decreased immunity, sexual dysfunction and decreased fertility [6].

Various stress stimuli may interfere with gonadal function. Stressors may include physical, chemical, biological, social and psychological factors. The latter two may lead to reduced sperm count and sperm mobility, abnormal sperm morphology, erectile dysfunction, ejaculation disorders, reduced libido, changes in the levels of gonadotropins, testosterone, prolactin and other hormones [7, 8]. These abnormalities are not restricted to humans but have been observed in all the higher animals [9]. Based on observations of experimental animals, it has been suggested that sexual behaviours and reproductive activities are particularly susceptible to the effects of stress and, in particular, to the consequences of the antagonism between glucocorticosteroids and the hypothalamic-pituitary-gonadal axis hormones [10].

Whatever the nature of the stimulus, stress leads to stimulation of the central nervous system (CNS) and changes in the secretion of neurohormones. Stimulation of the hypothalamic-pituitary-adrenal (HPA) axis (corticotropin-releasing hormone [CRH], antidiuretic hormone [ADH], adrenocorticotropic hormone [ACTH]) is characteristic, and leads to changes in the secretion of hormones of the adrenal medulla and cortex.

The key role is played by CRH, which activates the sympathetic system in addition to affecting the HPA axis. CRH is a peptide produced in the periventricular nuclei of the hypothalamus. The hormone reaches the anterior lobe of the pituitary gland and activates transcription of the gene encoding proopiomelanocortin (an ACTH precursor). CRH acts through two types of receptors: CRH-R1 receptors, which predominate in cortico-limbic structures, and CRH-R2 receptors, found in subcortical structures. They are also expressed in the adrenal medulla, prostate, intestines, spleen, liver, kidneys and testicles. The diversity of isoforms of the individual receptor subtypes is characteristic and determines the modulation of stress response at the local level. CRH-R1 receptors seem to play the principal role in anxiety reactions, while CRH-R2 receptors appear to be involved in vegetative responses [11].

Synergistic or additive effects have been demonstrated for CRH and ADH, a hormone produced in the periventricular nuclei which also stimulates the secretion of ACTH. Also, neuropeptide Y is an important regulator of stress reactions. By stimulating neurons that produce CRH, neuropeptide Y simultaneously suppresses the sympathetic system at the central level [3].

Fluctuations in the levels of glucocorticosteroids, adrenaline, noradrenaline, beta-endorphins, encephalins and sex steroids are observed during stress. Stress leads to reduced levels of melatonin and interferes with the circadian rhythm of its secretion. In stressful situations, reduced serotonin and increased dopamine levels are observed. The abnormalities involve mesocortical and mesolimbic elements of the dopaminergic system, which are stimulated by catecholamines, CRH and glucocorticosteroids [3].

CRH and catecholamines trigger secretion of beta-endorphins by the hypothalamus, which elevates the pain threshold and changes emotional responses. The increased secretion of beta-endorphins leads to increased secretion of prolactin (PRL) and somatostatin and to decreased secretion of growth hormone (GH).

Activation of the HPA axis decreases production of thyroid-stimulating hormone (TSH) and suppresses peripheral conversion of thyroxin to triiodothyronine.

The locus coeruleus and groups of catecholaminergic cells of the medulla prolongata and the pons play an important role in the body's response to stress. Neurons of the locus coeruleus are stimulated by changes in the internal milieu of the body (hypoglycaemia, changes of blood pressure and body temperature, changes in the volume of circulating fluids) and by purely psychological stimuli. Their activation stimulates, in turn, the hypothalamus, neurons secreting CRH, resulting in the secretion of noradrenaline in various areas of the cerebrum. One may note the fact that the limbic system and the hippocampus are actively involved in the processing of stress stimuli. Stimulation of the sympathetic system and the amygdala is fundamental to anxiety responses.

Reduced counts and/or suppressed activity of T cells, B cells and NK cells are also observed in individuals exposed to stress [3, 7].

Factors modifying the effects of stress

The number of factors that may modify the course of stress reactions is virtually unlimited. In the case of men, the following factors seem to play a more prominent role: race, age, marital status, siblings, educational background and income. Other factors include nationality and language, housing conditions, social environment and religiousness [12].

Men are believed to be less susceptible to psychological stress than women. A less pronounced tendency to depression and a limited susceptibility to disruption of interpersonal relations are thought to contribute to this phenomenon. The reasons may also include a more limited exposure to stressful situations (such as parental obligations or household chores). Intersexual differences in the perception of stress, and in admitting that one is being stressed out, may also partially explain it. Interestingly, married men report psychological stress in their lives less frequently than do unmarried men [13, 14].

A higher level of education and higher income are believed to be factors that protect against stress [15, 16]. Racial differences in the perception of stress have also been reported. Males of European origin suffer from psychological stress to a greater degree than Asians [15].

Psychological stress and the endocrine function of the testicles

The first stage of stress reaction involves activation of the adrenergic system, changes in mental functioning and changes in the functioning of the endocrine and immune systems.

Studies conducted in animals and observations in humans have demonstrated that stress inhibits the secretion of gonadotropins mainly through CRH and opioids (beta-endorphins). CRH increases the secretion of neuropeptides, such as ACTH, ADH, vasoactive intestinal peptide (VIP) and beta-endorphins [7]. CRH inhibits the function of neurons that release gonadotropin-releasing hormone (GnRH) directly and indirectly, via stimulation of the secretion of beta-endorphins. ACTH activates the HPA axis and increases the secretion of cortisol, which is responsible for a number of changes in the body's metabolism. It seems that chronically elevated cortisol level is a factor of particular importance for the function of male gonads [3]. Testicular function may also be modified by prolactin, interferon-γ, TNF-α and NK cells [3, 17].

Suppression of the pulsatile release of gonadotropins is, for instance, observed after an infusion of CRH [18], but also during fever or in depressive states. A similar effect is also exerted by interleukin-1 or a reduction in leptin levels. The effect of stress may be neutralised by using opioid receptor antagonists (e.g. naloxone). Interestingly, studies on a sheep model demonstrated that psychological stress decreased the amplitude of GnRH pulses, irrespective of cortisol action through type II glucocorticosteroid receptors [19].

It should be added here that local intratesticular production of catecholamines may suppress the production of androgens also through auto- and paracrine mechanisms [20].

Examples of stressful situations which result in anticipatory hormonal changes include surgery or parachute jumps. The latter are often used as stimuli in experimental studies of the mechanisms of psychological stress. In one investigation, testosterone levels measured in the saliva of parachutists (nine measurements between 8.00 am and 4.00 pm) were lower than those in the control group (individuals who did not jump) throughout the day on which the parachutists jumped. Particularly marked reductions in salivary testosterone levels were observed just before boarding the aircraft, while plasma testosterone profiles in the parachutists did not differ from those in the controls. It was surprising that the levels of testosterone and cortisol did not change over the four hours between the morning sampling and the boarding. A significant increase in the level of LH was observed following the jump [21].

In perioperative stress, which depends on the extent and duration of the procedure, reduced testosterone levels may persist for as long as three weeks after surgery [22].

According to the biosocial model theory, in men who win, testosterone levels increase and cortisol levels decrease, while in men who lose, the changes are the opposite (testosterone levels decrease and cortisol levels increase) [23]. In studies investigating the relationship

between stress and endocrine response, levels of hormones were determined in the blood and saliva, e.g. of athletes pursuing various sports disciplines. Not all the studies have confirmed the above phenomenon, and in many studies the differences in hormone levels between the winners and losers were statistically non-significant [6]. It has been pointed out that factors that could significantly affect the endocrine response in such circumstances include the athlete's ranking position, previous winning experience, and fitness level.

It has been reported that testosterone levels may decrease in situations of stress associated with participation in military training or direct involvement in combat [7]. However, another study found no significant abnormalities of the hypothalamic-pituitary-gonadal axis in soldiers exposed to submaximal exertion in the form of a four-day march with a load of 10 kg for a distance of 185 km [24].

The level of testosterone may also be abnormal in representatives of stressful professions. Swedish authors measured testosterone levels and carried out semen analyses in 44 men of various professions. The samples were evaluated every three months over a period of one year. The results suggested that total (but not free) testosterone levels might be decreased in periods of greater mental stress in men leading sedentary lifestyles. No such relationship was, however, observed in men who performed jobs that entail physical exertion [25].

Authors from the Krakow infertility clinic [26] analysed the relationship between hormonal parameters and stress (qualified on the basis of ACTH levels) in a group of 83 men. They hypothesised that increased exposure to stress corresponded with higher ACTH levels. The study showed that the higher the ACTH levels, the higher the levels of LH, but also the levels of testosterone. Testosterone levels in subgroups identified on the basis of ACTH levels (5–10, 11–30 and 31–50 pg/ml) were: 437.13 ± 235.14, 486.35 ± 214.47, and 528.50 ± 277.41 ng/dl, respectively.

The European Male Ageing Study investigated, among other parameters, the relationship between the body's hormonal status and stress. A total of 1,600 men aged 40 to 79 years were enrolled in the study. The prevalence of stress associated with sexual activity was similar in the subgroups of men with high and low levels of total, free and bioavailable testosterone [27].

A prospective study of 430 Danes evaluated the effects of psychological stress on hormonal parameters, seminologic parameters and fertility. Also in this study, the researchers failed to identify any relationship between the level of stress and the levels of hormones (LH, FSH, inhibin B, testosterone and oestradiol) in men, and the effects on fertility were negligible [28]. The same authors also excluded any relationship between professional stress and plasma hormone levels in men [29].

The results of the observations cited above show that the relationship between psychological stress and endocrine gonadal function is unclear.

Psychological stress and spermatogenetic function

The efficacy of spermatogenesis in humans is several times lower than that in, for instance, rodents. Under physiological conditions, about 30–50% of the sperm cells show structural abnormalities and a reduced fertilising capability [30]. Severe stress may suppress spermatogenesis, as evidenced by testicular biopsies in prisoners awaiting the verdict [31].

Stress often leads to the abatement of the pulsatile release of gonadotropins and an associated hypoandrogenaemia. In addition to the well-known effects through the central nervous system, CRH and beta-endorphins, stress also exerts its effects by local action of CRH and beta-endorphins on the testes. There is no clear evidence of any effects of stress on the function of the Sertoli cells [28].

Stimulation of the autonomic nervous system may affect ejaculate volume, sperm concentration and, most probably, sperm motility (variable amount of secretions of the accessory sex glands). The detailed mechanisms of these interactions are unclear [7, 32].

In an American study, spermiograms were assessed every two weeks over six months in 28 healthy volunteers. A negative correlation between stress level and ejaculate volume, and between stress level and percentage of normal sperm cells, was observed [33].

A study of a group of 225 infertile men also demonstrated that stress was one of the factors that negatively correlated with seminologic parameters. 80% of the study subjects admitted to being in a stressful professional or personal situation, which was associated with abnormal morphology and reduced viability of their sperm cells. The authors suggested a possible relationship between these abnormalities and elevated prolactin levels [34].

Further evidence for the effect of stress on spermatogenetic function is provided by the observation of 27 men inhabiting an area affected by an earthquake (Kobe, 1995). Reduced motility without changes in sperm concentration was observed in ten men whose houses had been completely or partially destroyed. These abnormalities resolved within no more than nine months after the event. No changes in seminologic parameters were observed in men who were in areas where the magnitude of the earthquake did not exceed 4 on the Richter scale [35].

On the other hand, an unexpected finding of increased sperm count and improved sperm motility was observed in medical students during the exam period [36].

Table II. *Comparison of various life events as sources of psychological stress (selected on the basis of [38])*
Tabela II. *Porównanie różnych wydarzeń życiowych jako źródeł stresu psychologicznego (wybrane na podstawie [38])*

Severity of stress	Life event	Severity of stress	Life event
100	Death of a spouse	45	Retirement
73	Divorce	36	Change to different line of work
65	Separation	29	Child leaving home
63	Death of a close family member	28	Outstanding personal achievement
53	Personal injury or illness	20	Change in residence
50	Marriage	13	Holiday
47	Dismissal from work	12	Christmas

A prospective study of 157 men (aged on average 33 years) demonstrated that neither having a stressful job nor experiencing divorce/separation were associated with significant changes in semen parameters. The only changes observed involved reduced sperm motility, reduced percentage of sperm cells showing forward movement, and changes in the morphology of the sperm heads in men who had experienced death of a close person [37]. According to the Holmes and Rahe stress scale [38], death of a close one is considered to be one of the strongest life stressors (Table II).

It has been proposed that emotional stress accompanying infertility treatment may negatively affect spermatogenetic function [31].

In a study of 500 men participating in an *in vitro* fertilisation (IVF) procedure, for instance, baseline values of semen parameters (qualification for treatment), such as: sperm concentration in 1 ml, total sperm count and sperm motility, were higher than those directly preceding insemination (following oocyte aspiration). During the preparation for IVF, the category of spermiograms in 21 men changed from normal to pathological, and considerably increased the risk of IVF failure [39].

On the other hand, the authors of a prospective Danish study did not observe any relationship between psychological stress and semen quality in 430 men trying for a first baby using natural methods. The study, however, showed that the likelihood of conception was lower in 77 men who were exposed to greater stress and who concomitantly had sperm counts below 20 million/ml [28].

Another study, which enrolled 1,076 infertile couples, assessed the effect of stress on semen quality and fertilisation capability. A positive correlation was demonstrated between sperm concentration and well-being index. Suspected depression led to reduced sperm concentration. No relationship was observed between psychological factors and rapid forward movement or morphology of the sperm cells [40].

The relationship between stress and sperm quality was also analysed in a cross-sectional cohort study of 744 men who, along with their partners, attended antenatal clinics in five American cities. No medical interventions were performed in the subjects. After eliminating confounding factors, the authors showed that experiencing two or more stressful situations increased the likelihood of reduced sperm concentration (log scale, $\beta = -0.25$, 95% confidence interval [CI] –0.38 to –0.11), reduced the percentage of viable sperm cells ($\beta = -1.95$, 95% CI –3.98 to 0.07), and increased the number of sperm cells showing abnormal morphology ($\beta = -0.59$, 95% CI –1.48 to 0.30) [41].

The above findings are consistent with the results of a recently published meta-analysis of 57 cross-sectional studies of 29,914 subjects in 26 countries worldwide. This meta-analysis showed that psychological stress correlated with reduced sperm concentration (–23.01, 95% CI –41.06 to –4.96), reduced sperm motility (–6.49, 95% CI –10.20 to –2.78), and an increased number of sperm cells showing abnormal morphology (7.43, 95% CI 2.66 to 12.21) [42].

Conclusions

Psychological stress interferes with the endocrine and spermatogenic function of male gonads.

Stress-induced hormonal changes depend on the severity and nature of the stressor, duration of exposure to the stressor, and the baseline condition of the body. In chronic situations, these may lead to hypogonadotropic hypogonadism.

Stress-induced disorders of spermatogenesis are most commonly manifested by reduced sperm concentration and motility and increased percentage of sperm cells of abnormal morphology.

The above attempts at generalisation must, however, be treated with caution, as the effects of stress are largely dependent on individual responses.

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