Review Article

Stress and hormones

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ABSTRACT

In the modern environment one is exposed to various stressful conditions. Stress can lead to changes in the serum level of many hormones including glucocorticoids, catecholamines, growth hormone and prolactin. Some of these changes are necessary for the fight or flight response to protect oneself. Some of these stressful responses can lead to endocrine disorders like Graves' disease, gonadal dysfunction, psychosexual dwarfism and obesity. Stress can also alter the clinical status of many preexisting endocrine disorders such as precipitation of adrenal crisis and thyroid storm.

Key words: Graves' disease, hormones, stress

Introduction

'Stress' may be defined as any situation which tends to disturb the equilibrium between a living organism and its environment. In day-to-day life there are many stressful situations such as stress of work pressure, examinations, psychosocial stress and physical stresses due to trauma, surgery and various medical disorders. In this review, we will highlight in brief the hormonal changes in stress and its impact on the endocrine system with particular emphasis on Graves' disease.

Hormonal Changes During Stress

In response to stress, the level of various hormones changes. Reactions to stress are associated with enhanced secretion of a number of hormones including glucocorticoids, catecholamines, growth hormone and prolactin, the effect of which is to increase mobilization of energy sources and adapt the individual to its new circumstance.

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Cortisol

Activation of the pituitary-adrenal axis is a prominent neuroendocrine response to stress, promoting survival. Stimulation of this axis results in hypothalamic secretion of corticotrophin-releasing factor (CRF). CRF then stimulates the pituitary to adrenocorticotropin (ACTH), 8-lipotropin and 3-endorphin. Plasma levels of these hormones can increase two- to fivefold during stress in humans.[1] The paraventricular nucleus of the hypothalamus is responsible for the integrated response to stress.[2] Norepinephrine, serotonin and acetylcholine mediate much of the neurogenic stimulation of CRF production.[3]

Catecholamines

Stimulation of the pituitary-adrenal axis is associated with release of catecholamines. This leads to increased cardiac output, skeletal muscle blood flow, sodium retention, reduced intestinal motility, cutaneous vasoconstriction, increased glucose, bronchiolar dilatation and behavioral activation.[4] Timio *et al.*,[5] have reported increased activation of the adrenosympathetic system during occupational stress.

Vasopressin

Acute stress leads to rapid release of vasopressin from the paraventricular nucleus of the hypothalamus along with corticotrophin releasing hormone CRH. Vasopressin can

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stimulate secretion of ACTH from the pituitary by acting on the V1b receptor, potentiating the effect of CRH. During chronic stress with corticotroph responsiveness there is preferential expression of hypothalamic vasopressin over CRH.[6]

Gonadotropins

In stress there is suppression of circulating gonadotropins and gonadal steroid hormones leading to disruption of the normal menstrual cycle.[7] Prolonged exposure to stress can lead to complete impairment of reproductive function.[8] Gonadotrophin releasing hormone GnRH drive to the pituitary is decreased, probably due to increased endogenous CRH secretion.

Thyroid Hormones

Thyroid function is usually down-regulated during stressful conditions. T3 and T4 levels decrease with stress. Stress inhibits the thyroid-stimulating hormone (TSH) secretion through the action of glucocorticoids on the central nervous system.[9]

Growth Hormone

The growth hormone (GH) level is increased during acute physical stress. The level can increase up to two- to tenfold. Because of its insulin-antagonistic effect, GH may enhance metabolic activity. In psychological stress, however, GH responses are rarely seen.[10] Rather there is GH secretory defect with prolonged psychosocial stress.[11]

Prolactin

Depending on the local regulatory environment at the time of stress, prolactin level can either increase or decrease. Vasopressin and peptide histidine isoleucine may be involved in the secretion of prolactin during stress.[12] However, the teleological significance of change in the prolactin level is uncertain. It may affect the immune system or some aspect of homeostasis.

Insulin

Insulin may decrease during stress. This along with increase in its antagonistic hormones can contribute to stress-induced hyperglycemia.[13]

Stress as a Precipitating Factor/Cause of Endocrine Disorders

Hyperthyroidism

The relationship between stressful life events and the onset of Graves' disease (GD) was initially documented by Parry in 1825. There is data available on the high incidence of thyrotoxicosis among refugees from Nazi prison camps. Psychological distress has been reported in up to 65% of younger patients with hyperthyroidism and physical stress in many older patients.[14] The term 'Kriegsbasedow' was coined following the observation of increased incidence of GD during major wars. Many epidemiological studies have demonstrated that patients with GD had more stressful life events than control subjects prior to the onset or diagnosis of Graves' hyperthyroidism and that stress had an unfavorable effect on the prognosis of GD. A study by Winsa *et al.*, has indicated that negative life events may be a risk factor for GD. Compared with controls, newly diagnosed Graves' patients claimed to have had more negative life events in the 12 months preceding the diagnosis, and negative life-event scores were also significantly higher (odds ratio 6.3, 95% confidence interval 2.7-14.7, for the category with the highest negative score).[15] Sonino *et al.*, in Italy examined 70 patients with GD and a control group of 70 healthy subjects and reported that patients with GD had significantly more positive and negative life events than controls (patients 1.51 total events, controls 0.54; $P< 0.001$). They investigated the occurrence of stressful life events in the year before the first sign of disease onset.[16] Kung *et al.*,[17] from Hong Kong and Radosavljevi´c *et al.*,[18] from Yugoslavia also reported association of negative life events with GD. In the study by Yoshiuchi *et al.*, a positive correlation between stress and GD was found in female patients, but not in male patients.[19] Patients with GD not only had a significantly greater number of stressful life events but also a higher number and greater impact of negative stressful life events compared to patients with toxic nodules and normal controls.[20] Paunkovic *et al.*, reported a significant increase in the incidence of GD in Eastern Serbia during the civil war.[21] However, most of the studies are retrospective case-control studies and it is quite difficult to evaluate the effect of a given stressful event in different individuals. Moreover, the accuracy in filling self-rated questionnaires or answering standardized interviews may vary widely among patients due to different emotional impact. Therefore, it is difficult to definitely rule out the effect of possible mild, still undiagnosed thyroid hyperfunction already present in the examination period.

Genetic factors such as HLA (Human leukocyte antigen) and CTLA-4 (Cytotoxic T lymphocyte antigen – 4) determine the susceptibility to GD.[22] Stress may lead to immunologic perturbations and may affect the immune response to TSH receptor through modulation of hormones, neurotransmitters and cytokines. A defect of antigen-specific suppressor T-lymphocytes has been

proposed to be partially responsible for the initiation of GD.[23] Stress may result in a defect in the immunologic surveillance leading to production of TSH receptor antibodies.[24] In genetically susceptible individuals stress favors the development of GD by shifting the Th1-Th2 immune balance away from Th1 towards Th2.[25] This shifting may affect the onset or course of GD.

However, there are many studies which failed to show any relationship between stress and GD. No significant difference was seen in the number and nature of stressful life events up to six months before the onset of thyrotoxicosis between patients with thyrotoxicosis and nontoxic goiters in the study by Gray and Hoffenberg.[26] Chiovato *et al.*, could not find past or present Graves' hyperthyroidism in patients with panic disorder.[27]

Diabetes Mellitus

Severe stress may be a risk factor for diabetes. Children aged five to nine years with stress were significantly more likely to be diabetic.[28] However, recent-onset Type 1 diabetics, 15-34 years old reported no major stress factors within the year before diagnosis.[29] Thus stress in early life may be a risk factor for diabetes, but not in young adults.

Gonadal dysfunction

In females stress can lead to anovulation, amennorhea and other menstrual irregularities. Among newly incarcerated women with stress 9% had amenorrhea and 33% had menstrual irregularity.[30]

In males, there can be decreased sperm count, motility and altered morphology.[31] Ejaculatory disorders, impotence and oligospermia may be associated with psychological factors in male infertility.[32]

Psychosocial dwarfism

This is an extreme form of failure to thrive and may be associated with dramatic behavioral abnormalities. Defective GH secretion has been reported with stimulation test. Reversal of GH insufficiency within three weeks of removal from hostile environment has been reported.[11] Munoz-Hoyos *et al.*, observed a conspicuous reduction in the levels of neuroendocrine markers (melatonin, serotonin, β-endorphins and ACTH) in children suffering from affective deficiency, a diminution which was even more noticeable in the children presenting delayed growth. The organic incapability of confronting stress on a genetic basis, and/or the fact of repeated stresses, from exhaustion of the homeostatic mechanisms, could make some groups of patients liable to suffer depressive symptoms associated with a wide range of deleterious consequences in the endocrine system leading to delayed growth.[33]

Obesity

Mental stress leads to chronic activation of the neuroendocrine systems. Cortisol favors central fat deposition, a decrease in the adipostatic signal leptin and an increase in the orexogenic signal ghrelin, inducing increased appetite and food intake. This phenomenon contributes to the current epidemic of obesity. The "stress" genes which have been selected under pressure in ancient environments may have not adapted to the rapid environmental changes of today.[34]

Impact of Stress on Preexisting Endocrine Disorders

Poor glycemic control

In adults the relationship between stress and poor diabetic control is well established.[35] Poor metabolic control has also been reported in children and adolescents with Type 1 diabetes with stress.[36]

Addisonian crisis

Patients with adrenal insufficiency because of various etiologies may develop adrenal crisis on exposure to stress. To prevent this, the replacement doses of steroid need to be doubled during the period of stress.[37]

Thyroid crisis

Thyroid storm may be precipitated by physical stress. Acute emotional stress can also precipitate thyroid storm.[38] Yoshiuchi *et al.*, observed that those patients with GD who were stressed for six months after beginning of therapy were significantly and independently associated with the hyperthyroid state 12 months after beginning therapy.[39] Fukao *et al.*, studied the effects of emotional stress and patients' personality traits on the prognosis of hyperthyroidism in 69 antithyroid drug-treated euthyroid patients with Graves' hyperthyroidism. They observed a higher frequency of relapse in those who had stress.[40] A retrospective study by Benvenga on GD found that those who had taken benzodiazepine only in the acute phase of thyrotoxicosis relapsed more compared to those who had taken benzodiazepine for a longer period.[41] Vos *et al.*, observed that stress exposure is not related to the biochemical severity of GD, but is directly related to the clinical severity of GD.[42]

Conclusion

In today's competitive modern world one encounters stress in various aspects of life. As an adaptive response to stress, there is a change in the serum level of various hormones including CRH, cortisol, catecholamines and thyroid hormone. These changes may be required for the

fight or flight response of the individual to stress. However, long-term exposure to stress may lead to many deleterious consequences leading to various endocrine disorders. Also, stress leads to change in the clinical course or status of many endocrine conditions.

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