Chronic Stress, Neuroendocrine Disorders and Metabolic Syndrome

Stresul cronic, perturbările neuroendocrine şi sindromul metabolic

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Abstract

More than 50 years ago clinicians had suggested that frequent association of obesity with arterial hypertension and with atherosclerotic vascular disease should involve some common pathogenic mechanisms including certain neuroendocrine disorders – a hypothesis being now supported by experimental and by clinical case-control studies. Daily cortisol secretion measured in saliva had higher levels in subjects at high stress comparativeley to subjects at low stress. A case control study emphasized that when compared to controls, the subjects displaying features of the metabolic syndrome were also presenting higher urinary elimination of cortisol and catecholamines metabolites, as well as higher serum levels of interleukin - 6 and CRP. It was therefore concluded that autonomic, adrenocortical and inflammatory causes are involved in the development of metabolic syndrome, which can be a intermediate on the pathway between long term psychosocial stress and coronary artery disease. Visceral obesity may be a target of activated sympathoadrenal system, as adipose tissue of such patients is endowed with numerous highly sensitive β3 adrenoreceptors. Subsequent activation of hormone dependent lipase within this hypertrophic adipose tissue would trigger the release of fatty acids into the portal flow leading to hepatic steatosis and insulin resistance. Free fatty acids taken up into specific receptors would stimulate the synthesis of plasminogen activator inhibitor -1 (PAI-1). The interaction of free fatty acids derived from a high fat diet with a G protein-coupled transmembrane receptor (the GPR-40, preferentially expressed on pancreatic β cells) would mediate an excessively increased glucose stimulated insulin secretion, leading to hyperinsulinemia and metabolic syndrome. Beta –adrenergic stimulation would also activate the renin-angiotensin–aldosterone system within adipose tissue of obese patients. Visceral obesity and neuroendocrine disorders are also involved in the pathogenesis of renal disease and in the hyperinsulinemia of women with polycystic ovary syndrome. Elucidating the pathogenesis of metabolic syndrome should promote the initiation of novel therapeutic approaches.

Keywords: *stress, hypothalamic-pituitary-adrenocortical axis, metabolic syndrome, cortisol secretion, adrenergic stimulation, visceral obesity, free fatty acids, polycystic ovary syndrome*

Rezumat

În urmă cu peste 50 de ani clinicienii au sugerat că asocierea frecventă a obezităţii cu hipertensiunea arterială şi bolile coronariene ar putea implica mecanisme patogenice comune, incluzînd unele perturbări neuroendocrine - ipoteză susţinută actualmente de studii experimentale şi clinice. Secreţia circadiană de cortizol măsurată în salivă a avut nivele mai mari la subiecţii supuşi unui stres intens faţă de cei expuşi la stres mai

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redus. Un alt studiu a demonstrat că la subiecţii cu sindrom metabolic există eliminări crescute în urină a cortizolului şi a cataboliţilor catecolaminelor, precum şi nivele serice crescute de IL-6 şi CRP, ajungându-se la concluzia că stimulări simpatoadrenergice, adrenocorticale şi inflamatorii sunt implicate în apariţia sindromului metabolic, care ar putea fi o verigă intermediară între stressul psihosocial de durată şi coronaropatii. Obezitatea viscerală poate fi o ţintă pentru sistemul simpatoadrenergic, dat fiind că ţesutul adipos al acestor subiecţii conţine numeroşi β3 adrenoceptori. Activarea consecutivă a lipazei hormonodependente în acest ţesut adipos hipertrofiat produce eliberarea acizilor graşi liberi în fluxul portal, conducând la steatoză hepatică şi insulinorezistenţă. Acizii graşi liberi captaţi de receptori specifici stimulează sinteza inhibitorului activatorului plasminogenului-1 (PAI-1). Interacţiunea acizilor graşi liberi cu un receptor transmembranar cuplat cu o proteină G (GPR-40, exprimat preferenţial pe membranele celulelor beta pancreatice) mediază o secreţie excesivă de insulină stimulată de glucoză, conducând la hiperinsulinemie şi sindrom metabolic. Stimularea beta adrenergică activează şi sistemul renină-angiotensină-aldosteron din ţesutul adipos al pacienţilor obezi. Obezitatea viscerală şi perturbările neuroendocrine sunt de asemenea implicate în patogeneza bolilor renale şi în hiperinsulinemia femeilor cu sindrom de ovar polichistic. Elucidarea patogenezei sindromului metabolic poate contribui la noi abordări terapeutice.

Cuvinte cheie: *stress, axa hipotalamo – pituitară- adrenocorticală, sindrom metabolic, secreţie de cortizol, stimulare adrenergică, obezitate viscerală, acizi graşi liberi, sindrom de ovar polichistic*

Keenly observant clinicians perceived and reported more than 50 years ago on a frequent association of overweight, arterial hypertension and coronary heart disease, occurring in subjects submitted to sustained stress in relation to changes in the life style, and especially in those experiencing difficulties to adjust to the new conditions and to efficiently perform the required professional duties. It was therefore considered that such a morbid association may not be merely casual and that some common pathogenic mechanisms, including certain neuroendocrine disorders may be involved (1).

In the absence of data on the biochemic pathophysiology of adipose tissue and on mechanisms relating psychosocial stress to endocrine disorders and to subsequent metabolic abnormalities, such a hypothesis may have appeared rather hazardous. Evidence accumulated during the last 30 years justify this point of view, and some authors wonder whether the metabolic syndrome may not be a neuroendocrine disorder (2).

Actually, more than 70 years ago Selye (3) recognized the paradox that the physiologic systems activated by stress can not only protect and restore but also damage the body. Because the most common responses to stress are mediated through the activation of hypothalamic – pituitary – adrenocortical axis (HPA axis) and of the autonomic sympathetic nervous system, recent research was focused on the behavior of these systems in conditions of sustained stress.

Stress related cortisol

It should be mentioned that chronic stress is produced by a summation of low intensity but repetitive effects of a stressor. In order to perceive changes occuring during a day at work or at home it was necessary to devise a procedure for obtaning data on cortisol secretion while avoiding the unfamiliar milieu of a hospital including repeated venipunctures. Cortisol in saliva meets such required circumstances. Actually, saliva cortisol measures free circulating cortisol and is independent of changes in saliva secretion (4, 5). Using this approach, Bjorntorp and Rosmond (2) emphasized that in the absence of stressful conditions the cortisol secretion occuring in healthy subjects is highest in the morning, progressively decreasing and becoming minimal in the evening , with a transient increase related to lunch. In opposition to this normal diurnal curve, the secretion of cortisol occuring in patients with visceral obesity and metabolic syndrome, as well as in some endocrine disorders (low levels of testosterone, and/or of growth hormone), is charac-

terized by low morning and lunch values and by a slower decrease towards evening, the cortisol secretion displaying a low variability (2).

In relation to high stress (subjectively evaluated), the saliva cortisol level increases and remains increased during the day. Persistently increased cortisol secretion may be the result of an impaired feedback mechanism aimed at attenuating the response to stress. Actually receptors to glucocorticoids (GR) were detected in the hippocampus and forebrain (temporal lobe) involved in the control of HPA axis (6-8). Evidence was also provided that serotonin mediators may participate in this neurocircuitry (6-9) and an experimental removal of GR in the brain of rats led to the development of symptoms rather similar to those noted in depressive humans (10). Noteworthy a deficiency of such GR occurring in patients with depression would result in uncontrolled secretion of cortisol eventually exerting noxious effects. Actually women with a history of depressive illness were found to have decreased bone mineral density because chronic moderately elevated cortisol concentrations inhibit bone formation (11).

Persistent activation and activity of HPA axis may eventually lead to its exahaustion and to a compensatory activation of the sympatho - adrenal system (6). This activation may contribute to hypertension and enhanced mobilization of free fatty acids from adipose tissue thus favouring the developement of atherogenic dyslipidemia (12). Chronic stress and disordered endocrine system may also be involved in the pathogeny of accelerated aging, impaired immunity and impaired memory (13).

Neuroendocrine disorder and metabolic syndrome

Although the relationship between chronic stress, neuroendocrine disorder and cardiovascular disease can not be denied, the relative importance and the sequence of the various pathogenic factors and mechanisms differ according to the authors' views. For example Reaven (14) considers that insulin resistance caused by genetic abnormalities and environmental factors (unhealthy proatherogenic diet, smoking, alcohol) would lead to an activation of the autonomic sympathetic nervous system and the subsequent arterial hypertension and atherogenic dyslipidemia.

Other authors (15) consider that adrenocortical, autonomic and inflammatory causes would synergically contribute to the developement of metabolic syndrome and that interactions between these pathogenic factors would reciprocally potentiate their effects. Actually a clinical case-control study performed in Great Britain (15) demonstrated that subjects displaying features characteristic for the metabolic syndrome were also presenting increased urinary elimination of cortisol and catecholamine metabolites, as well as higher plasma levels of C reactive protein (CRP) and of interleukin 6 (IL-6). These findings point to the association of a smoldering inflammatory process to an activation of the hypothalamic - pituitary – adrenocortical (HPA) axis, as well as of the authonomic sympathoadrenergic system. In keeping with such case control data, experiments performed on rats submitted to physic stressors (electric shocks at the paws) or psychological ones (conditioned reflexes) led to an activation of the HPA axis along with increased plasma levels of intereleukin 6 (16). This proinflammatory cytokine's plasma levels also increased after a pharmacological β adrenergic stimulation in humans (17). Based on such data Yudkin (18) considers that IL-6 could be the link between obesity, stress and coronary artery disease, while Brunner and coworkers (15) feel entitled to state that the metabolic syndrome could be an intermediate on the pathway between long - term psychosocial stress and coronary artery disease.

Hormones control metabolic processes by modulating enzymatic activities

Modulation of enzymatic activities by hormones is exerted by two main mechanisms:

1. increasing or decreasing the number of molecules for a certain enzyme by stimulating or inhibiting its synthesis as well as by limiting the

proteolytic degradation of the protein – enzyme
2. modifying the catalytic efficiency of each enzyme molecule by accelerating or by delaying the transformation of the inactive zymogen into an active enzyme, or by modifying the enzyme's affinity for its physiologic substrate.

Evidence had been provided that steroid hormones penetrate into cells up to the nucleus, modulating the transcription of genes thereby inducing the synthesis of certain enzymes while depressing the production of other enzymes.

For example, glucocorticoid hormones induce enzymes involved in gluconeogenesis, such as pyruvate carboxylase, phosphoenolpyruvate carboxykinase and diverse aminotransferases, while insulin would repress these enzymes' synthesis and would induce glucokynase and glycogensynthetase thereby enhancing glucose utilization and storage. Other hormones, such as catecholamines, glucagon, vasopresin, luteinizing hormone (LH) and follicle stimulating hormone (FSH), activate adenylatecyclase connected to cell receptors specific for the above mentioned hormones. Adenylatecyclase would subsequently split ATP releasing cyclic adenosyl monophosphate (cAMP) which is known to stimulate the phosphorylation of certain enzymes thereby activating hepatic phosphorylase and initiating glycogenolysis, while inhibiting glycogen synthetase (19, 20). Such examples are illustrative for the role of hormones in the regulation of metabolism and may explain the developement of metabolic abnormalities related to endocrine disorders.

The pathogenic role of visceral (intra-abdominal) obesity

It is now clear that expansion of adipose tissue seen in obesity results in more blood vessels, more connective tissue fibroblasts and especially more macrophages including bone-marrow derived monocytes. Evidence had also been provided that adipose tissue is an active and complexe endocrine organ that secretes numerous bioactive substances, including hormones, growth factors and cytokines, in addition to releasing free fatty acids (21).

Visceral obesity, one of the components of the metabolic syndrome is also an established cardiovascular risk factor. To be mentioned that this adipose tissue is provided with abundant β3 adrenoceptors highly sensitive to adrenergic stimulation (22), which would trigger the activation (by phosphorylation) of the hormone dependent lipase enhancing the release of free fatty acids (FFA). The release of FFA into the portal flow is accompanied by the release of monocyte derived proinflammatory cytokines (TNFα, IL-6), directly reaching the liver and being involved in the development of hepatic steatosis and of nonalcoholic steatohepatitis (NASH) also contributing to the pathogeny of metabolic syndrome (23, 24). It should be specified that adipocytes are the source of adiponectin and of leptin, while the proinflammatory cytokines are released from the monocytes infiltrated into visceral adipose tissue (21).

Besides being a target of stress activated sympathoadrenal system, adipose tissue was found to be endowed with enzymes actively contributing to hormone disorders. It was actually demonstrated that the adipose tissue of obese women displays elevated levels of mRNA for 11 β hydroxysteroid dehydrogenase (11B HSD) involved in the generation of cortisol by hydroxylating 17 hydroxyprogesterone, and also in the production of aldosterone by hydroxylating deoxicorticosterone (25). Evidence was also provided that the renin - angiotensin - aldosterone system (RAA) is present and active not only within the juxtaglomerular apparatus in the kidneys but also in myocardium and in brain (26), as well as in the adipose tissue (27), which is also endowed with angiotensin II receptors (28).

To be noted that β adrenergic stimulation was found to release renin (29), thereby initiating the production of angiotensin II involved in the pathogenesis of hypertension and also in the generation of reactive oxygen species (30).

Signaling through free fatty acids

Besides providing a major metabolic fuel (storage and transport of energy), fatty acids taken up into certain receptors would elicit specific responses with pathophysiologic relevance. These effects are dependent upon fatty acids' physical and chemical properties (i.e. whether saturated or unsaturated and in such case the number and even the localization of the double bonds). Certain polyunsaturated free fatty acids (PUFA) from fish oil are known to reduce cardiovascular risk.

Such PUFA n-3 are the eicosapentaenoic acid (EPA 20:5 n-3) and docosahexenoic acid (DHA 22:6 n-3). The first cipher indicates the number of carbon atoms, the second indicates the number of double bonds; notation n-3 also known as omega 3 indicates that the position of the last double bond involves the third carbon atom from the fatty acid's end terminated by a methyl group. For example, in the case of EPA with 20 carbon atoms, the last double bond is at carbon 17, while in the case of DHA with 22 carbon atoms the last double bond is at the carbon 19.

The binding of PUFA n-3 to some special receptors (the peroxysome proliferator activated receptors PPARs) would enhance hepatic oxydation of saturated fatty acids, thereby reducing plasma triglyceride levels (31, 32) while addition of PUFA n-3 to cultured adipocytes would reduce the expression of leptin and of resistin (32). It was also shown that a reduction of body fat mass by diet and exercise was accompanied by an increase in plasma adiponectin level (32).

Addition of some more common free fatty acids (mainly saturated) to cultured hepatocytes enhanced the synthesis of plasminogen activator inhibitor (PAI-1), a most important inhibitor of fibrinolysis, and evidence has been provided about a region in the human PAI-1 gene responsive to FFA (33, 34)

A pathogenic relevance is being recently attributed to the interaction of saturated free fatty acids with a G-protein transmembrane coupled receptor, the GPR-40, preferentially expressed in the pancreatic β cells (35). At increased plasma concentrations of FFA, related to a high fat diet, this receptor would trigger an exagerated glucose stimulated insulin secretion, leading to hyperinsulinemia (36), which would eventually result in obesity, hepatic steatosis, insulin resistance and metabolic syndrome. Mice lacking GPR-40 in the pancreatic β cells do not develop neither hyperinsulinemia, nor the metabolic syndrome when fed a high fat diet (35). Noteworthy, transgenic mice overexpressing GPR-40 within the pancreatic β cells showed decreased insulin secretion and developed diabetes, presumably owing to a lipotoxic effect on the pancreatic β cells (36).

The above mentioned experimental data are in agreement with previously reported observations emphasizing that acute enhancement of insulin secretion by FFA in humans is lost with prolonged FFA elevation (37) and are supporting the importance of β cells failure in the developement and progresion of type 2 diabetes (38, 39). According to a presumed scenario, signals elicited from disordered neuroendocrine systems may dysregulate enzymatic mechanisms and the resulting metabolites would then continue to emit pathogenically relevant signals. Such observations are highly suggestive that adiposity and neuroendocrine disorders are synergically contributing to the developement of metabolic syndrome and this scenario is illustrated by the study of the polycystic ovary syndrome.

Polycystic ovary syndrome (the Stein Levendhal syndrome)

This endocrine disease, often accompanied by insulin resistance and hyperinsulinemia is characterized by the bilateral presence of polycystic ovaries, ovulatory failure, infertility, hirsutism and obesity (sometimes). Clinically there is an overlap with the Cushing's syndrome and with the virilising ovarian and adrenal tumors. The diagnosis is usually established by imagistic methods (ecographic, endoscopic), while laboratory investi-

gations pertaining to virilization reveal levels of androstendione, testosterone and dehydroepiandrosterone (DHEAS) that are slightly above the upper limits of normal. Luteinizing hormone (LH) may be elevated but follicle stimulating hormone (FSH) is rather decreased, so that a ratio LH/FSH > 1,5 would support the diagnosis of polycystic ovary syndrome (PCO) (40). The relationship of PCO with metabolic syndrome is not yet completely elucidated as hyperinsulinemia had been detected not only in obese, but also in normal weight women with PCO (41). However, hyperinsulinemia is more accentuated in the obese and noteworthy, endocrine and ovarian function were improved during dietary treatment of obese women with PCO (42). It was also found that women with glycogen storage disease (GSD) given frequent carbohydrate rich meals (mainly uncooked starch) in order to prevent bouts of hypoglycemia, became overweight or even obese so that clinically silent PCO cases developed insulin resistance and hepatic steatosis (43, 44). One may presume that the increased plasma level of LH would enhance the synthesis of progesterone which within the luteal cells of PCO patients, expressing 17 hydroxylase would be transformed into 17 hydroxyprogesterone, this intermediate steroid then being transformed into cortisol within the adipose tissue of the obese PCO patients overexpressing 11 hydroxysteroid dehydrogenase (25).

Renal disease in obesity

While the role played by visceral obesity in the pathogenesis of cardiovascular disease had been extensively reported, there are rather few data on the occurence of renal disease in obese patients. The first sign of obesity induced renal injury is the presence of microalbuminuria especially when associated with hypertension. The progression of lesions towards a glomerulopathy with or without glomerulosclerosis would proceed somehow paralelly with the accentuation of disorders characteristic for the metabolic syndrome (atherogenic dyslipidemia, glucose intolerance, smoldering inflammation, hypertension). Proinflammatory cytokines released from monocytes infiltrated into adipose tissue, leading to endothelial dysfunction, exagerated ultrafiltration due to hypertension, activation of the renin-angiotensin-aldosterone system, the generation of reactive oxygen species and the prothrombotic state would synergically contribute to the progression of lesions. A peculiar pathologic condition providing additional pathogenic mechanisms is represented by renal lithiasis occuring more frequently in obese patients, as their eliminated urine is more acid and richer in uric acid, oxalate and calcium (45, 46).

The most severe renal disease associated with metabolic syndrome is diabetic nephropathy rapidly progressing to end stage renal failure (ESFR).

Therapeutic attempts based on progress achieved in unravelling pathogenic mechanisms

A direct intervention on the HPA axis may involve the risk of unwanted effects, and attempts to modulate this axis by acting on centers within the brain are not convincing. Actually inhibition of CB1 receptors of the endocanabinoid system by the synthetic compound rimonabant was found to reduce food intake and weight gain, while independently of this effect an accelerated oxidation of fatty acids and an improved lipoprotein pattern were also obtained (47). Unfortunately such a therapy was reported to elicit symptoms of anxiety and depression in some patients (48). Surprisingly, in an article published in Archives of Internal Medicine, the authors claim that „transcendental meditation" (TM) practiced for 16 weeks led to a normalization of blood presure, as well as significantly reducing insulin resistance and sympatho-adrenergic activity (49). Even if the authors gave no details about this type of meditation, one may nevertheless presume that TM may have reduced the drive to greedy acquisitiveness for material goods and would also have attenuated the ambitions elicited by the excessively competitive modern society.

A procedure more accessible to the busy modern people might be the therapy with inhibitors of angiotensinogen converting enzyme (ACE inhibitors) which would not only reduce blood pressure, but would also delay the progression of atherosclerosis (50).

Noteworthy a population based study performed in England emphasized that people at a higher socioeconomic position were at a lesser risk for developing the metabolic syndrome (51, 52). One may presume that such persons are more likely to acquire knowledge concerning cardiovascular risks and to adopt a healthy lifestyle.

Abbreviations

ACE = angiotensinogen converting enzyme,
CRP = C reactive protein,
DHEAS = dehydroepiandrosterone,
ESFR = end stage renal failure,
FFA = free fatty acids,
GR = receptors to glucocorticoids,
GSD = glycogen storage disease,
HPA = hypothalamic - pituitary – adrenocortical,
11β HSD = 11 β hydroxysteroid dehydrogenase,
PCO = polycystic ovary syndrome,
PPARs = peroxysome proliferator activated receptors,
PUFA = polyunsaturated fatty acids,
TM = transcendental meditation

Addendum

Several months after having submitted the manuscript, relevant data associating depression to the metabolic syndrome became known to us and are presently mentioned below:

Lupu D, Surdea Blaga T, Dumitraşcu DL. Depresia - un marker psihosocial al sindromului metabolic. Clujul Medical 2011, 84(3): 402-6.

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