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Review

Steroid hormones interrelationships in the metabolic syndrome: An introduction to the ponderostat hypothesis

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SEXUAL DIMORPHISM IN THE METABOLIC SYNDROME

The clairvoyant early implication of sex hormones in the characterization of the metabolic syndrome (MS) was detected early,[1] and in accordance with the well-known sex-related main patterns of fat deposition in obesity: gynoid and android.[2] The differences point to a direct implication of androgens and estrogens in the development, properties and maintenance of obesity and, by extension, to the cumulus of diseases grouped in the MS.[3,4] For a long time, the key issue of the MS, i.e. the metabolic event explaining (and justifying) most of the derangements of the MS, has been considered to be insulin resistance.[5,6] Later, the emphasis was directed to a lower molecular level, the inflammatory response of tissues, mainly white adipose tissue (WAT);[7] this response was assumed to be mediated principally by cytokines.[8] Currently, however, the number of research fronts open is considerable, with the emphasis on mechanistic molecular-level analyses.[9] The widespread focus on the signalling pathways to account for the modulation of physiological changes and the commencement of pathological derivation[10,11] has, to a certain degree, caused us to lose some fundamental perspective. The processes at the molecular level never occur in an 'ideal' isolated setting, but are intricately involved in multiple metabolically and structurally complex systems, i.e. in cells which communicate with other cells within the same tissue, organ or at a systemic inter-organ level. There are several layers of superimposed (and completely intergraded) regulatory systems which contain fail-safe mechanisms to prevent catastrophic events in order to efficiently maintain life.

When we analyse the MS from a strictly physiopathological point of view, the most striking effects observed are those defined in the *deadly quartet*: obesity, hypertension, insulin resistance and hyperlipidemia.[12] However, in this context, the term *obesity* is often further defined as *upper body* or *visceral obesity*.[13] This is an important point. Many obese women show a fairly normal metabolism, lacking a full manifestation of the MS,[14,15] but in a high proportion of men, *visceral* obesity, even of limited extent, is often accompanied by the full manifestation of the MS associated diseases.[16] There is obviously a significant number of obese individuals who simply store more fat in their bodies without significant inflammation, insulin resistance, hypertension etc.;[15,17] this type of obesity may reach high proportions of body fat, but it is often deposed in a lower body fat deposition (largely subcutane-

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ous) pattern.[17] In contrast, android obesity is more harmful, even with markedly lower proportions of body fat.[18] It is obvious that fat storage alone cannot constitute the basis of the MS pathology.[19] Indeed, the reverse is true, since there are individuals with all the symptoms of a developed MS who show a body fat content within normalcy and who are oxymoronically defined as *normal-weight obese.*[20,21]

In general, women tend to show a dispersed distribution of fat most of which is located in the subcutaneous space, whereas in men a large part of the fat is concentrated within the abdominal cavity.[22] In rodents, the differences are less marked, since a considerable amount of fat is stored in the abdominal space in the retroperitoneal and perigonadal pads, which cannot be equated with the omental fat of humans;[23] it is hypothesized that rat mesenteric fat is closer in pathogenic potential and metabolic activity to human visceral fat.[24]

In any case, we should distinguish two main types of obesity, android and gynoid, based on the distribution of fat, the overall metabolic transcendence of excess fat and the severity of its health consequences. The implication of steroid hormones characterizes this large difference.[25,26] There is a high degree of superposition between the two main types of fat distribution, but in most cases the consequences can easily be derived from changes in sex hormone availability.[27]

Estrogens tend to limit body fat deposition,[28,29] and when there is ample fat storage under their aegis, its distribution adopts the gynoid pattern.[30,31] At menopause, when estrogen synthesis and levels sharply decrease, a redistribution of body fat occurs, diffusing the contours of the gynoid pattern towards a hybrid android-influenced pattern.[32] This change has been attributed to a shift in the imbalance between androgens and estrogens.[33]

Androgens facilitate muscle and bone growth and maintenance[34,35] and are also assumed to promote the male-related android distribution of body fat.[36] However, testosterone diminishes the accumulation of intra-abdominal fat.[37] In fact, visceral fat is a major site for androgen inactivation,[38,39] thus the fight is two-sided. In the MS, testosterone administration tends to lower body fat,[40] and hypoandrogenism[41] or androgen deprivation treatments are correlated with marked increases in fat deposition, both visceral and subcutaneous.[42]

Hypoandrogenism (i.e. low levels of serum testosterone) is a common finding in the MS,[41,43] usually paired with decreased dehydroepiandrosterone (DHEA) levels[44] and lower synthesis/levels of androstenedione and testosterone.[45,46] Serum testosterone activity may be even lower because of its binding to SHBG [47,48] (sex hormone-binding globulin) and other testosterone-binding proteins,[49] including CBG[50] (glucocorticoid-binding globulin). The generalized hypoandrogenemia observed in male obesity[51] is compounded by an increased aromatization of androgens to estrogens, especially in the enlarged adipose tissue[52] of the obese individual, producing estrogens[53] and thus inducing estrogenization. Obesity favours this decrease in androgens by activation of the expression of aromatase,[54] which adds to the large mass of adipose tissue, but also because of the targeted destruction of androgens.[38,39,50] Inhibition of aromatase in obese men helps reverse their altered hypothalamus-pituitary-gonadal axis towards androgen normalization.[55]

STEROIDS AND MS

Role of androgens in the pathophysiology of MS

Our blueprint for development sets the timing for the establishment of a number of changes in body function, shape and patterns of activity and behaviour inherited from our ancestors. The sex-related differences in fat distribution have a strong behavioural and sexual component; they have been well described for groups of gorillas,[56] but are also – in part – applicable to humans. These changes (body shaping, baldness and/or graying hair in males) occur slowly, following a gene-controlled pattern [57] over a prolonged period of time, at specific points of the life-cycle and parallel to sex hormone synthesis (and levels).[58,59] The process is controlled by the brain, mainly through hypothalamic control of gonadotropin secretion by the hypophysis, which regulates androgen and estrogen levels and follows precisely established developmental patterns based on genetics[60] and seasonal and circadian rhythmicities.[61] The timing and extent of changes are also regulated by energy availability (e.g. by leptin secretion by WAT stores[62,63]) and other environmental factors (e.g. through cortical signals, glucocorticoids,

etc). Nevertheless, they always result in long or very long-term changes following the evolutionary blueprint for reproductive effectiveness and group survival.

The implication of estrogens and androgens in the development of the diseases associated with the MS was recognized very early, even before the term *inflammation* was applied in this context.[31] A telltale sign of their implication is the growing incidence of the polycystic ovary syndrome,[64] largely due to an alteration in androstenedione metabolism,[65] but characterized by insulin resistance,[66] low adiponectin[67] and a number of MS-related pathological traits.[68-70] Polycystic ovary syndrome is a component of the MS.[71,72] Central to polycystic ovarian syndrome is an altered metabolism of androgens.[73-75] Polycystic ovary syndrome is usually treated with metformin,[76] an insulin sensitizer not affecting androgen metabolism.

It has been established that the different pathological traits of the MS are present with varying intensity in different individuals, with predominance of diabetes, atherosclerosis, obesity, etc., often with non-pathological degrees of some of the diseases of the syndrome, although in some cases the full spectrum of diseases is evident. Polycystic ovary syndrome may be one such MS manifestation,[72] this hypothesis largely based on its superimposed symptoms.[77-79] It should be noted here that MS affects not only the female reproductive system but also the male. Indeed, MS in males causes hypoandrogenism,[41,80] with decreased testosterone[81,82] as well as adrenal weak androgen dehydroepiandrosterone DHEA levels.[83,84] Thus, in both sexes the MS is associated with altered androgen metabolism.[80,85-87]

The imbalance between lower androgens and raised corticosteroids signals a permanent shift in metabolic priorities: androgens are highly anabolic, increasing protein preservation and skeletal (muscle, bone) growth,[88-90] whilst glucocorticoids promote protein degradation (to fuel gluconeogenesis, thus maintaining euglycemia) and induce skeletal regression, including loss of minerals from bone and generalized wasting.[91-93] Androgens are natural antidepressants,[94-96] and excess of glucocorticoids is associated with depression,[97-99] another example of the antagonistic roles these steroid hormones play, at least in the brain, which in fact controls everything else in all physiological mechanisms.

Role of estrogens in the pathophysiology of MS

To produce estrogens we need first to synthesize androgens, starting with dehydroepiandrosterone; the last step being aromatization[100,101] (Figure 1). Thus, the decline of DHEA caused MS may in the end diminish the estrogen-mediated beneficial effect on vascular endothelium integrity[102] and defence against superoxidation.[103] Estrogens also ameliorate insulin resistance[104] and facilitate the handling of low-density lipoproteins by the liver.[105,106] Estrogens play a protective role in the brain,[107,108] the vascular tree[109,110] and indeed in most other tissues, which is compatible with their profound effects on fat metabolism.[111,112] The decline of estrogen levels following menopause[113] results in a rapid weakening of these protective roles, altering the equilibrium with androgens, especially in individuals not on estrogen-replacement therapies.[114] This is not akin to androgenization, since the decline of estrogens is followed by a fall in androgens. Estrogen replacement therapy may indeed deepen the deficit of androgens[115] by stimulating shared inactivation paths. However, the loss of sex steroids equilibrium seems to be mainly an imbalance of both androgens and estrogens against corticosteroids. The decline in estrogen levels may well be the result of the loss of androgens.[113]

The ponderostat hypothesis

Estrone is a powerful anabolic hormone, promoting growth and the deposition of fat in the young,[116] but is a fairly inactive estrogen.[117] Estrone is synthesized in significant amounts by WAT,[100,118] which stores it largely as its oleoyl-ester,[119,120] a precursor of a postulated ponderostat signal.[121]

The ponderostat system (Figure 2) regulates lipid storage to an optimally adjusted mass, but the MS rapidly alters the pre-established ponderostat settings in such a way that either the brain becomes less sensitive to the signal(s) from WAT or this tissue shows a decreased capability to synthesize the signalling molecule(s). In any case, we may say that in obesity, the brain has lost its ability to control the size of WAT,[122] probably because of inadequate sensing of adipose tissue actual size due to either lower levels or insensitivity to ponderostat signals. The case of the active form of oleoyl-estrone is paradigmatic, since

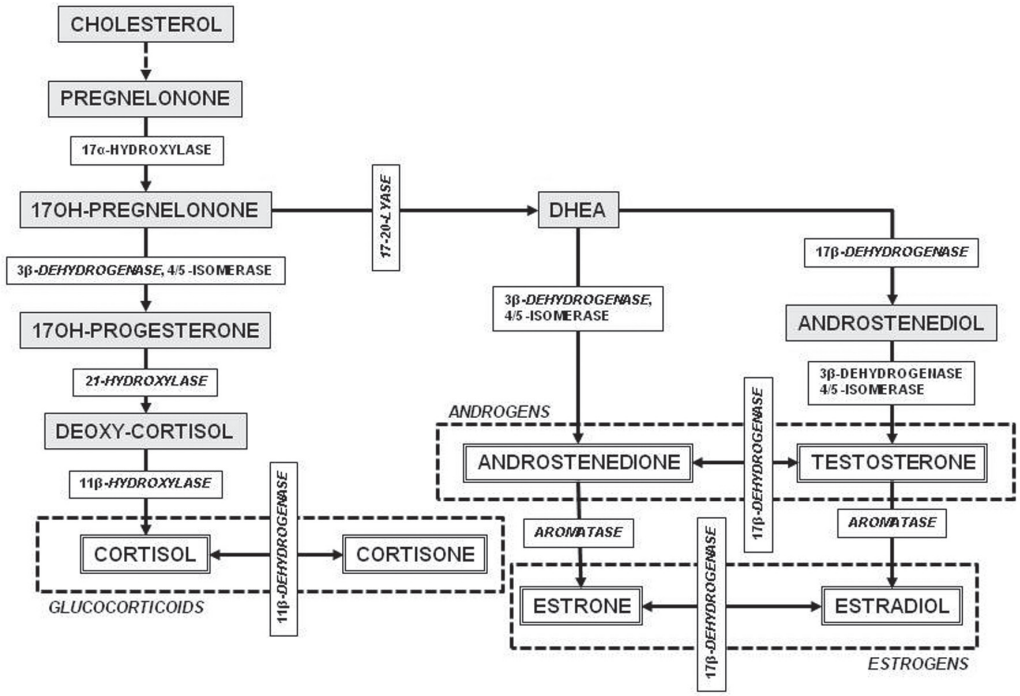

Figure 1. Metabolism of steroid hormones. Relationships between the main glucocorticoids, androgens and estrogens.

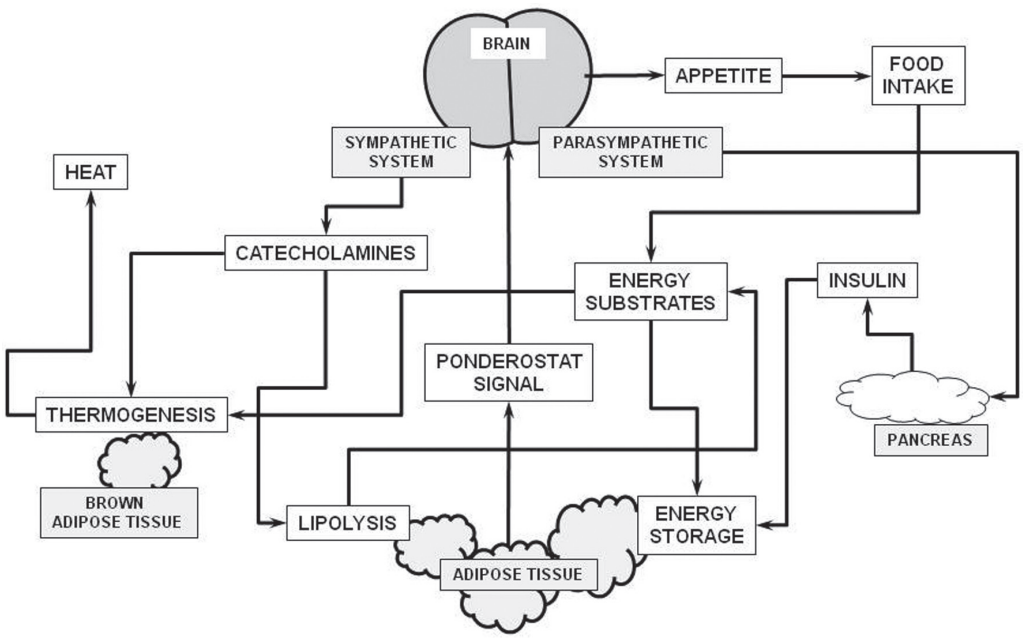

Figure 2. Schematic representation of the ponderostat model. The "ponderostat signal" is released into the bloodstream proportionally to the mass of energy stored in adipose tissue. The brain recognizes its level and associates it to age, sex and energy availability. If the amount of fat reserves is inadequate, the brain can increase the availability of substrates largely through control of appetite (and thus food intake) and the action of the autonomous nervous system. A perceived lack of energy increases food intake and the secretion of insulin, resulting in an overall increase in energy storage in adipose tissue. Conversely, perceived excess energy stored in adipose tissue elicits a decrease in food intake, but also a sympathetic response, increasing lipolysis. In this manner, a larger proportion of available energy substrates is endogenous and may be used by brown adipose tissue (and other organs/tissues) for thermogenesis and its final elimination as heat.

most of the damages caused by the MS are decreased or minimized by the pharmacological administration of this oleoyl-estrone, derivative and postulated precursor of a ponderostat signal.[123]

Ponderostat settings are subjected to the changes in body weight reserves pre-established by our genes, epigenetic modulations and developmental influences, and shift throughout our entire life. One of the most dangerous effects of the MS is precisely the changes it induces in our ponderostat settings. Obese individuals encounter all types of physiological difficulties when trying to lose weight[124-126] largely because their ill-adjusted ponderostat setting is *defended* by the body mechanisms that prevent the loss of its reserves. Our lack of knowledge on how the ponderostat sequence of events works and how it is set up makes us uncertain as to the importance of this mechanism with regard to MS manifestations.[127] Glucocorticoids may play a role in the maladjustment of the ponderostat setting, both because of their omnipresence in the MS[128-130] and their role, as yet little known, in the control of androgen and estrogen metabolism,[131-134] which may extend to its counteracting effects upon the estrone-derived ponderostat signal candidate.[135]

Role of glucocorticoids in the pathophysiology of MS

It is clear that androgens and estrogens cannot alone account for the ravages and, especially, the timing of appearance of the associated pathologies of the MS. However, there is a third and critical element in the equation: corticosteroids, and mainly glucocorticoids. The implication of glucocorticoids in obesity are well known.[136-138] Specifically, the main enzyme converting cortisone (less active) and cortisol (active), type 1 11β-hydroxysteroid dehydrogenase, is present and functional in WAT[139,140] (Figure 1). This allows adipose tissue to generate active cortisol from circulating less active cortisone.[141,142] Cortisol is essentially the product of the cortex of the adrenal glands, which also produce aldosterone,[143] dehydroepiandrosterone (DHEA)[144] and lesser amounts of sex hormones.[145] Glucocorticoids play a crucial role in the control of homoeostatic stability: they induce resistance to insulin[146,147] and other hormones and cytokines[135,148] (including glucocorticoids themselves[149]) and enhancement of liver gluconeogenesis,[150] largely at the expense of body protein;[151] they also mobilize minerals from the bone,[152] hamper the full immune response to real (or feigned) aggressions,[153] favour lipid deposition[147] and help the body to recover after any physical exertion or stressful situation (exercise, exhaustion, infection, stress, etc.).[154,155] These roles are critical for survival and thus take precedence over the more slow effects of sex hormones, which effects become more extended over time.[156] The immediacy of glucocorticoid action, however, is not absolute, especially when we compare it with actions as fast as these of catecholamines whose effects start in the split-second range (i.e. fight-or-flight situations);[157] glucocorticoids act at a slower pace, but nevertheless much faster than the longer periods needed for many of the actions of estrogen and androgen to manifest.[158,159]

In the MS, the hypothalamus-pituitary-adrenals axis is more active than under normal conditions[160] and there is a close relationship between obesity and stress.[161,162] However, the circulating levels of cortisol in MS are often within the normal range,[163] since part of the modulation of corticosteroid action depends on the peripheral conversion (i.e. within the same target tissue) of cortisone and of the less active cortisone.[164,165] There is also a complex control of hormone availability through variability of both its transport in blood compartments and attachment to cells largely through CBG.[166,167]

An additional third level of regulation arises from the formation of dimeric structures by steroid hormone receptors,[168,169] which enables the chimeric formation of hybrids of glucocorticoid-bound receptors with other ligands such as androgens,[170] estrogens[171] and retinoids.[172]

Glucocorticoids inhibit the synthesis and activity of androgens.[173-175] However, androgen precursor DHEA (and, consequently, precursor of estrogens[176]) has anti-glucocorticoid activity.[177,178] Glucocorticoids may hamper the activity of estrogens. [179] It should be noted here that activation of the estrogen receptor affects the brain glucocorticoid receptor-dependent effects in the amygdala and in the neuroendocrine system are opposed.[180] However, glucocorticoids and estrogens may also act synergistically. Indeed, estrogens and glucocorticoids inhibit endothelial vascular

cell adhesion molecule-1 expression and suppress vascular endothelial inflammation.[181,182]

The glucocorticoid relationship with androgens is perhaps more antagonistic because of their different effects at the cellular level: androgens as enhancers of protein synthesis are powerful anabolic agents,[183] and corticosteroids tend to mobilize protein[184,185] to reap enough gluconeogenic substrates for the maintenance of glycemia.[186] Excess glucocorticoids (often at pharmacologic levels) induce protein, glycogen and mineral wasting.[92]

In the climacteric transition, women's synthesis of estrogen decreases[187] and a few *androgenic* effects appear, such as the redistribution of body fat[188,189] and weight increase[190] as well as the loss of most of the protective effects of estrogen on the brain, skin and cardio-circulatory systems.[191,192] There is a relative increase in androgens at menopause,[193,194] but glucocorticoid activity is also increased.[195] The transformation in body fat redistribution and increased deposition during menopause appears to be a consequence of a transient androgen increase and a slow but steady rise of the circulating glucocorticoids.

One of the main health problems associated with menopause, bone demineralization,[197] is a telltale indicator of both low estrogens and high corticosteroids, especially the latter. In males, this demineralization occurs at a slower pace, even in obese individuals with low levels of circulating testosterone.[198] It seems that even low androgen levels may be sufficient to prevent or limit osteoporosis. Consequently, it is not logical to attribute the change of gynoid to android (or intermediates) fat distribution patterns at menopause to *androgenization*. If there were indeed sustained androgen activity increases, the bone may be effectively protected as in men. Meanwhile, the conversion of androgens to estrogens, albeit limited, should help further protect bone minerals. The effects observed in post-menopausal women are not, thus, only attributable to an imbalance between estrogens and androgens but mainly between estrogens and glucocorticoids.

GLUCOCORTICOIDS, INFLAMMATION AND MS

The deranged actuation of the immune system may also be at the root of a number of MS-related diseases such as psoriasis[199,200] and other autoimmune pathologies.[201] Probably, the excess proinflammatory cytokine production of inflamed cells induces an excessive stimulation of the defence system.[202,203] The actual absence of real enemies of the immune system to efficiently fight, as well as the lack of coordination of the estrogen and glucocorticoid secretion and function, may enhance the levels and activity of the latter. The higher incidence of a few types of cancer (excluding those related to food consumption[204]) in obesity and the MS[205,206] corroborate this interpretation.

The change in microbiota composition elicited by excess secretion of nitrite into the digestive system[207] may also combine with a strong and activated immune system[208] to modify the intestinal interface with the microbial symbiotic biota.[209] This question has barely been analysed, except for the verified differences in the species distribution of the microorganisms, confirming what is known about *obese microbiota,*[210,211] which is fairly independent of the type of food consumed[212] and is very different from the *normal microbiota* in species distribution and proportions. The existence of low, albeit constant, levels of lipopolysaccharide in the blood of obese individuals[213] suggests that a low-level intensity microbial-induced inflammation may be a significant cause of the inflammatory response observed in the MS.[214] However, there are other plausible explanations, such as the great predominance of glucocorticoids, secreted in response of an enhanced immune system activity,[153] acting on the control of the bacteria kept at bay in the intestine,[215] or an excessive monocyte and macrophage phagocytic response to infection releasing residual lipopolysaccharide into the bloodstream.[213]

BRAIN PONDEROSTAT SETTINGS AND MS

The most elusive (and least known) effects of the MS occur in the brain; they can be arbitrarily divided into a number of superimposed actions:

a) modulation of the ponderostat size of body fat reserves (changes in ponderostat setting, modulation of food intake and modulation of energy expenditure)
b) effects on rhythms, sleep and meal patterns
c) effects on thymic and reward circuits

d) modulation of hormone secretion

e) changes in the pattern (blueprint) for the life-cycle

f) alterations of behaviour

Evidently, the modification of the ponderostat setting is a powerful tool for the epigenetic adaptation to environments with low food availability, since a higher setting results in higher efficiency in food energy utilization and the storage of fat when the energy is available. This trait (thrifty phenotype[216,217]) is a direct cause of obesity under conditions of excess available food energy. However, the consumption of a very rich diet for a long time (e.g. cafeteria diet[218,219]) also *disrupts* the adjustment of the ponderostat and results in obesity[220] without the epigenetic preparation for hard times ahead. It may be speculated that the ponderostat setting may be altered by metabolic or hormonal signals. It is difficult, however, to determine how, since we do not know for certain which is (are) the adipose tissue signal(s) that inform the brain of the mass of stored energy.

Obese persons retain a considerable ability to maintain their body weight,[221,222] albeit in a high, non-physiological setting. Hypocaloric diets have a limited effect in the obese[223,224] because in the end the body tries to regain the preset mass of reserves[225] and the ponderostat system forces the metabolic paths to save energy and store it to maintain the pre-established levels (ponderostat setting). The ponderostat works mainly by establishing an equilibrium between energy intake (appetite) and energy expenditure (complemented by the modulation of thermogenesis)[226] (Figure 2). Appetite is largely controlled by the hypothalamus through two confronted systems: NPY as main food intake promoter[227,228] and melanocortins as inhibitors.[229,230] Significantly, the precursor of melanocortins, proopiomelanortin, is also a precursor of endorphins and ACTH corticotrophin.[231] Melanocortin signaling is also related to melanin deposition in the skin[232] (it intervenes in the development of *acanthosis nigricans,*[233] a complication of diabetes[234]). Melanocortin is closely functionally related to orexins[235] which intervene in the establishment of the complex network controlling food intake.[236] Orexins are also implicated in the regulation of sleep and sleep cycles.[237]

OTHER ASPECTS OF THE BRAIN – ADIPOSE TISSUE INTERACTION

There is a direct relationship between sleep and the development of the MS.[238,239] Sleep deprivation induces MS-like disturbances;[240,241] in general, obese individuals sleep less time than non-obese[242,243] and the deleterious effects of sleep apnoea are not only the consequence of the catecholamine surges but mainly of the loss of sleep quality.[244] The sleep changes observed in the MS are also related to the alteration in circadian feeding and activity rhythms found in obesity[245] and which are largely regulated by ACTH corticotropin / corticosteroids.[246] The loss of rhythms favours increased (unscheduled) food intake and the nibbling of food results in a disarranged meal feeding structure,[247] which adds to the behavioural and neurochemical alterations associated with the MS.

It is important to note that in a small area of the lower brain (hypothalamus and surrounding structures) a large part of the control of food intake is concentrated,[248] including, most probably, the adjustment of the ponderostat setting, the control of thermogenesis, sleep and circadian rhythms and the regulation of the hypophysis, which in turn controls most of the endocrine axes that regulate the function of the thyroid, adrenals, gonads and the water, mineral and electrolyte equilibrium.[249-251] These mechanisms should be considered together with the direct influence on the autonomous nervous system functions (control of digestive tract motility, thermoregulation, heart rate, arterial tension and hemodynamic changes, to cite a few).[252-254]

The centres controlling the nervous system mechanisms of reward (dopamine, endorphins)[255] are close to and in direct relation with the hypothalamus,[256,257] which is also under the more or less direct control of cortical (voluntary) and sensorial areas,[258,258] including interoceptors detecting the status of intestine replenishment (and the nature of its contents),[259] glycemia,[260] blood acid-basic equilibrium, oxygen and osmotic pressure.[261,262]

Pharmacology gives us a number of possible clues to the function of the system. If cortical hedonic signals decrease by applying a pre-established hypocaloric diet, the increase of serotonin signalling helps reduce

body weight (dexfenfluramine, sibutramine)[263,264] in a process akin to the treatment of depression (fluoxetine, sertraline).[265,266] Again, glucocorticoids counter these effects and induce depression,[267] which may be counteracted by serotonergic stimulation.[268] The implication of cannabinoid receptors[269] (rimonabant is an inverse cannabinoid CB1receptor blocker[270]), and catecholamines (amphetamine inhibiting food intake[271] and phentermine or ephedrine increasing energy expenditure[272]) shows that the mechanisms controlling food intake and energy output, i.e. the ponderostat-driven mechanisms to regulate body energy, are multiple, complex and intertwined.

There are a number of drugs that cause iatrogenic obesity, including synthetic glucocorticoids,[273] adrenergic blockers[274] and a number of drugs used for psychiatric disorders.[275,276] The discontinuation of nicotine stimulation in smokers produces a significant increase in appetite and permanent weight gain[277] and the improvement of a number of psychiatric conditions results, again, in overweight.[278] Sometimes it It is difficult to distinguish between iatrogenic effects and normalization, i.e. suppression of a continued non-physiologic stimulus such as nicotine.

Surprisingly, the relationship of the MS with eating disorders is less manifest. A number of obese individuals present the psychological characteristics of binge eating,[279,280] but this may be a result of a cooperative cause, overeating, that has brought them to obesity,[281] scaled up to the MS as a consequence, not the other way around.[282] This may also be a consequence of unchecked stress that is compensated by *comfort feeding*.[283,284]

In sum, there is considerable evidence linking the different diseases and symptoms attributed to the MS, essentially in a web-like manner, resulting in the self-maintenance of most pathological traits. The increased knowledge of pathogenic paths only tends to strengthen the conclusion of the existence of a powerful linkage between the MS components.[10,285,286] Nevertheless, two major issues challenge this general view: a) the lack of identification of a hierarchical line-up of the diseases, with a clearly identifiable origin for the whole MS pathology tree and branches, and b) the extreme resilience of the system to therapeutic intervention.

CONCLUSIONS

The evidence linking the function of androgens, estrogens and glucocorticoids with the MS is abundant and consistent.[287]

Glucocorticoids: The full development of the MS pathologies is enhanced by glucocorticoids. Glucocorticoids suppress inflammation, a central characteristic of MS, and keep the immune system at bay. However, glucocorticoids provoke insulin and leptin resistance, which aggravates the already altered energy handling control of the MS, favouring fat synthesis, protein mobilization and increased liver glucose output. Glucocorticoids also alter the ponderostat setting, thus influencing the deposition of fat both through the loss of insulin control of glycemia, increased lipogenesis and energy availability and deregulation of the ponderostat system.

Androgens, on the other hand, tend to protect body protein and maintain growth: they are probably major glucocorticoid antagonists. Patients with MS pathologies are prone to hypoandrogenism in parallel to hypercortisolism.

Estrogens are critical for control of inflammation because of their protective and antioxidant properties. They are more potent than androgens when countering the combined effects of inflammation and glucocorticoids and are thus able to maintain a more robust resistance to the MS manifestations in females than that evident in males (Table 1). At menopause, however, the differences tend to disappear because of the fall in estrogen.

In summary, the equilibrium maintained in conditions of basal health conditions between androgen, estrogen and glucocorticoids are deeply altered by the dietary and environmental causes of the MS, establishing the preponderance of glucocorticoids over the other steroid hormone types as the main factor responsible for the appearance of its related pathologies. The marked differences in MS manifestations between females and males and the increasing rates of appearance (and severity) with advancing age (and losses of androgen and estrogen) help reinforce this hypothesis.[287]

Table 1. Summary of the main differences/relationships between glucocorticoids, androgens and estrogens

	Glucocorticoids	**Androgens**	**estrogens**
Active/less active forms	cortisol/cortisone *corticosterone/dehydrocorticosterone*	testosterone/androstenedione	estradiol/estrone
Main transporting protein in plasma	CBG	SHBG *(not in rodents)*	
Effects on body protein	wasting	increasing deposition and stores	protecting their integrity
Effects on carbohydrate metabolism	increase liver glucose output; increase glycemia; glycogen wasting		
Effects on lipid metabolism	increased overall lipogenesis from glucose and amino acids; enhanced lipid storage	limited lipid storage	decrease lipid storage; protection of lipids from oxidation
Effects on energy metabolism	favour lipids at the expense of carbohydrates and protein; alter the ponderostat setting	increase thermogenesis	increase thermogenesis; precursors of postulated ponderostat signal
Effects on mineral deposition in bone	mobilization (up to osteoporosis)	maintenance / retention	
Actions on inflammation	decrease (cytokine inhibition); synergistic effect with estrogens	decrease?	decrease (antioxidant); synergistic effect with glucocorticoids
Effects on the immune system	depress	enhance (protein/energy availability)	
Effects on insulin	induce insulin resistance	synergistic effects with insulin favouring protein deposition and growth	counteract glucocorticoid effects on insulin
Effects on steroid hormone synthesis and function	strongly inhibit androgen synthesis and actions; also (less strongly) estrogen action	block some glucocorticoid effects; DHEA is an antiglucocorticoid	decrease androgens (substrate for their synthesis); block some glucocorticoid effects

CBG: corticosteroid-binding globulin; DHEA: dehydroepiandrosterone; SHBG: sex hormone-binding globulin.

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