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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Estrogens and the regulation of glucose metabolism

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Abstract

The main estrogens: estradiol, estrone, and their acyl-esters have been studied essentially related to their classical estrogenic and pharmacologic functions. However, their main effect in the body is probably the sustained control of core energy metabolism. Estrogen nuclear and membrane receptors show an extraordinary flexibility in the modulation of metabolic responses, and largely explain gender and age differences in energy metabolism: part of these mechanisms is already sufficiently known to justify both. With regard to energy, the estrogen molecular species act essentially through four key functions: (1) Facilitation of insulin secretion and control of glucose availability; (2) Modulation of energy partition, favoring the use of lipid as the main energy substrate when more available than carbohydrates; (3) Functional protection through antioxidant mechanisms; and (4) Central effects (largely through neural modulation) on whole body energy management. Analyzing the different actions of estrone, estradiol and their acyl esters, a tentative classification based on structure/effects has been postulated. Either separately or as a group, estrogens provide a comprehensive explanation that not all their quite diverse actions are related solely to specific molecules. As a group, they constitute a powerful synergic action complex. In consequence, estrogens may be considered wardens of energy homeostasis.

Key Words: Estrogens; Insulin; Estrogen receptors; Energy metabolism; Glucose; Antioxidants; Metabolic syndrome

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Core Tip: Estrogens play a paramount and continued regulatory role, based on the synergy between the different forms of estrogen to maintain energy (and lipid/glucose) homeostasis. These functions include preventing: oxidative damage, lipid-induced inflammation, excess fat accrual and the complications of excess amino nitrogen. This short incomplete list is fairly close to a recipe for preventing the development of metabolic syndrome; abundant epidemiological and (partial) experimental data help

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support this assertion. We have to look more widely at estrogens (the different structural-functional types described in the text) to understand their extensive and powerful control of energy homeostasis.

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INTRODUCTION

The complex and growing implication of steroid hormones in homeostasis

Steroid hormones are derived from sterols, which play a critical role in the structure of the (mainly) eukaryotic membrane[1]. Most steroid hormones regulate animal functions, especially in vertebrates. Only recently, plant steroid hormone analogs such as the brassinosterols[2] have been found to play a significant role in the metabolic regulation in the most evolved plants[3,4]. Other steroids, including estrogens have also been found to act as regulators in some plants, but the information is still relatively scarce[5,6]. In addition, a number of higher plants are able to synthesize animal steroid hormones, such as testosterone and estrogens[7], as well as structural analogs which interfere with physiological functions and vital cycles of some animals [8,9], including direct allopathic interference[10]. The steroid hormone ecdysone is critical for molting of insects and other animals[11], and plants synthesize the analogs ecdysteroids to limit insect development[12].

Nevertheless, the most studied types of steroid hormones (estrogen, androgen, corticosteroid, progesterone) are typical and characteristic of vertebrates. However, the variability in functions, regulation and even mechanism of action is considerable, since the degree of implication of these hormones in the fundamental aspects of life: reproduction, feeding-growth-metabolism, neural and metabolic regulation, fall squarely in their fine tuning of life cycles, survival and evolution. Their effects, largely gene expression modulation, are being continuously uncovered, in a way that deviates from the classical distribution of functions for human steroid hormones, often presented as mere sex-definition signals or regulators of mineral and glucose homeostasis. The implication of all of these hormones in the defense mechanisms (including a massive implication in the immune system control[13,14] and optimization of metabolic function[15,16]) has been growing in importance in parallel to their development along the evolution path[17] that brought humans to their amazing homeostatic resilience.

This linear review is focused on estrogens, one of the most important vertebrate steroid hormone types, due to their critical function on the control of core metabolic partition in addition to their fundamental immune system control and reproductive functions.

The estrogens are not only “sex hormones”

Most of the investigations of estrogen effects on metabolic regulation, irrespective of sex, are fairly recent and notably skewed (Box 1). So far we have only limited information on the major role played by different forms of physiological estrogens in the control of energy metabolism at the whole body level[16,18].

The initially intense development of research on estrogens came to a climax by the mid XXth century[19,20], and was essentially focused on their pharmacology, as part of the development of combined estrogen-progestogen preparations for safe birth control in humans[21]. The studies on steroid hormones were not limited to estrogens (and progestogens), but were extended to androgens[22] and, especially, to glucocorticoids [23] through the development of a large number of synthetic drugs, widely used and which their development continues[24]. In a way, this expansion in the pharmacology of steroid hormones also provided considerable information on their mechanisms of action[25] and metabolism[26], including an extensive analysis of some possible complications of their clinical use[27-29]. Nowadays, the natural human corticosteroids (cortisol and cortisone, but also corticosterone[30]) are seldom prescribed, despite showing often quite different effects and pharmacological profile than the

myriad of synthetic corticosteroids in use[31]. The latter may bind to most of the natural receptors[32], but basically do not share the transporter proteins[33] or the inter-organ self-regulatory mechanisms of natural hormones (e.g. the hypothalamus-pituitary axis).

The common identification of “estrogen” with 17 β -estradiol (E2) and “androgen” with testosterone (T) is an inadequate oversimplification that helps to dismiss the regulatory and fine-tuning interrelationships of the different molecular species of estrogens, both with themselves or with androgens and other steroid hormones.

The estrogens are ancient regulatory agents, remarkably preserved along evolution. The number and structure of relevant molecules remains small and unaltered in spite of the variety and complexity of the mechanisms modulating their actions, somehow reflecting the cumulative experience (and expansion of metabolic interventions) acquired during evolution. The versatility of the nuclear receptors' modulation and signaling pathways allow the superposition of a dense web of signals, including fail-safe, duplicate, alternative and redundant mechanisms, which often make it difficult to find answers to the direct questions relevant to the clinicians.

The structures of estrogens

The principal distinguishing feature of animal estrogens is the phenolic nature of ring A, usually with a -OH in C3. No other type of steroid hormone contains a phenolic ring. The steroid nucleus of estrogens has 18 C, and lack a side chain. The main human functional estrogens are 3-hydroxy-17-keto-estrin (E1 estrone), 17 β estradiol or 3, 17 β -dihydroxy-estrin (E2 estradiol) and 3, 16 α , 17 β -trihydroxy-estrin (E3 estriol); during fetal development[34], another estrogen should be included: 3, 15 α , 16 α , 17 β -tetrahydroxy-estrin (E4 estetrol). Compared with all other mammalian steroid hormones, they are highly lipophilic (E1 > E2 > E3). This peculiarity facilitates their transport by lipoproteins[35] and binding to membranes[36] (including their crossing). The interactions with lipophilic entourage have been credited as a main factor for their effects on membranes[37] and mitochondrial function[38]. It is often assumed that estrogens are carried in the blood bound to proteins, largely sex hormone-binding globulin (SHBG), but the higher affinity and metabolic response to energy changes[39] of T (competing with E2 for SHBG) favors a closer dependence of the globulin levels and/or structure/affinity[40,41]. The much lower levels of E2 than T in plasma (both in women and men)[33] suggest that this dual (if real) transport of hormones may be a consequence of modulation of the molecular affinity of SHBG, in part through modification of its molecular weight[39,40,42]. The key factor is that under physiological conditions SHBG (or a varied group of SHBG isoforms) binds essentially T[39] and estrogen (almost 90% of plasma E2, but practically no E1[33]). In addition, the *in vitro* estrogenicity of E1 is considerably lower than that of E2[43]. This fact, together with the abundance of E1 in men (despite being an estrogen), and its high lipophilia resulted in a limited pharmacological interest for this molecule and a consequent lack of literature on it, and its function as a free hormone remains obscure. E1 is the most abundant estrogen in the body (when its esterified forms are included) [44], since it is produced (and stored[44]) in large amounts in white adipose tissue (WAT)[45]. Probably because of its lipophilia, a large portion of E1 in plasma is found esterified as sulfate, much more soluble than the free hormone[46,47], which facilitates its transport and eventual excretion. However, E1 can be made even more lipophilic by esterification with a fatty acid on C3[48] yielding acyl-estrone (AE1). In this form it has been found in lipoproteins[49] and adipose tissue[44]. AE1 are synthesized by adipocytes and modulated by leptin and insulin[50].

E2 is also esterified with fatty acids (acyl-E2 or AE2), becoming more lipophilic than E2, and thus also found in blood lipoproteins[51,52]. However, AE2 is largely esterified in C17 and not in C3 as are the AE1 esters[53]. This peculiarity of AE2 has been attributed to its higher capability to protect the lipids which surround the hormone from oxidation thanks to the unaffected phenolic -OH[51]. In any case, the highly lipophilic estrogens (through esterification with long-chain fatty acids) are a common occurrence for which no definitive function has yet been fully agreed upon, and which shows that the usual molecular species of natural estrogens, their transport in the bloodstream including their binding and physiological functions are far from being fully known. The high concentration of these varied estrogen-acyl-ester molecules in tissues, such as WAT[54] suggests a possible role of reserve or storage of preformed estrogenic molecules[53], which has been explained in part by the easiness of their synthesis by acyl-transferases, widely present in lipoproteins and tissues[55].

Main gender differences in human estrogen function

The scant number of in-depth non-clinical or pharmacological studies may be in part a consequence of the bias against estrogens (and of their bad name, Box 1). The reasons usually presented to sustain negative opinions, (which in the end limit metabolic analyses, and the eventual therapeutic use) are based largely on two factors: their known role as promoters of some forms of cancer, mainly breast[56] and endometrial [57], and a number of risks derived from their use[58,59] other than their assumed role as “female-linked” hormones. The essentiality of estrogens has been proven (in both sexes) for many functions, such as those related with sex differentiation and reproduction, as well as bone health[60]; but the key factor is the increasing flow of data that establishes a direct implication of estrogens in the control of the basic core of energy metabolism[16,61]. This control is affected by age, sex and diet; thus, the simpler division of steroid hormones function using a strict sex-oriented focus is no longer applicable. We simply need to know more about the estrogens and their functions, in exactly the same way as any other hormone, keeping in mind the species-specificity in some of their functions when establishing comparisons with animal models (Box 2).

Women have higher circulating levels of E2 than men, from puberty to menopause, with notable variation between physiological situations[62]. Men, even at their maximal reproductive capacity age, also show fairly high blood levels of E2[63]. There are not enough data on AE2 levels and distribution to establish valid comparisons, but it is probable that the parallelism will be maintained. On the other side, seldom clear gender differences are found in E1, the most abundant estrogen (free or esterified) in human blood. E1-sulfate (SE1) is subjected to a regulative “solubility/excretion” cycle [46] comparable to that of dehydroepiandrosterone[64]. The ample abundance of AE1 in tissues (rat) shows a more marked dependence on the mass of WAT than on sex[65].

T and E2 differently influence brain development from its earliest stages, both in the setting of its functional structure and -later- its psychological orientation and focus[66, 67]. The resilience of women against insulin resistance is higher than that of men[68, 69], at least until menopause[69]. Estrogen protects bone from demineralization in women and men[70,71], a function in part shared by T (at a lower potency, however [72]). The accrual and maintenance of body protein falls largely on androgens, mainly T[73,74], acting in a synergic way with growth hormone[75] and insulin[76] and countering the proteolytic capability of glucocorticoids[77]. The contribution of free estrogens to the maintenance of body protein mass seems to be more limited[78].

Estradiol signaling: classical nuclear receptors. Estrogen receptors α and estrogen receptors β

Thanks to their lipophilic nature, E2 (and E1) can easily cross membranes and bind specific estrogen receptors (ER) within the cell[79]. After dimerization[80] they are brought to the nucleus, where the complex E2-ER binds to deoxyribonucleic acid (DNA)[81] or to specialized proteins[82,83], eventually eliciting the expression or repression of specific genes. The nuclear-type estrogen receptors are highly complex [79,84]. Estrogen signaling, up to its final manifestation is not a fast process such as that of nervous or rapid-signaling chemical regulating agents (Box 3).

Binding to ER is, essentially, specific for the physiological estrogens[75,85], but a wide number of plant secondary metabolism compounds, synthetic non-steroidal estrogenic drugs and even some toxic industrial waste also bind the ER[86]. In humans, there are two main types of nuclear estrogenic receptors: estrogen receptors α (ER α) and estrogen receptors β (ER β)[87]. In fact, ER α and ER β are two families of related receptors, which maintain the same overall structure but not their complete sequence, the ERs being adapted, adjusted or changed for best effectiveness, in different tissues or because of changing needs[84,88].

The structures of ER α and ER β are shown in Figure 1. The main dominions are marked with letters (A to F), and correspond roughly (A/B) to a zinc finger and a binding site, activation function site 1 of the ERs (AF1); C is the place for binding estrogen-response elements (ERE) and then DNA[89]; D is a shorter sequence related to the binding of chaperone proteins and to the process of dimerization; and E/F is the ligand binding domain for estrogens and other factors, AF2[84]. The main ligands are the natural estrogens of mammals (E2, E1, E3 and E4), but some drugs, phytoestrogens [10], metals and diverse chemicals (xenoestrogens) can also bind the receptors[90]. Binding to the AF1 and AF2 may result in synergistic effects[91]. The length and distribution of ER parts may change within each receptor family depending on alternate sequences and splicing[84]. The affinity of ER α is maximal for E2, followed by E1, and that of ER β is also E2, followed by E3.

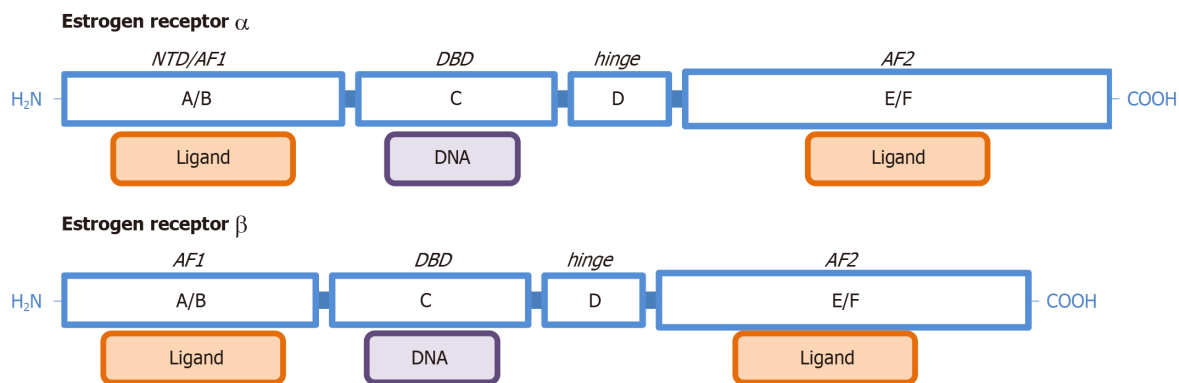


Figure 1 Functional structure of estrogen receptors α and estrogen receptors β . Domain names (A to F), and common denominations for the main functions are included: N-terminus domain; DNA binding domain, activation function site 1 of the estrogen receptors and activation function site 2 of the estrogen receptors. The graph is not drawn to scale and represents the complete (highest molecular weight) form for each of the two families of nuclear ERs. NTD: N-terminus domain; DBD: DNA binding domain; AF1: Activation function site 1 of the estrogen receptors; AF2: Activation function site 2 of the estrogen receptors.

The combination of affinities and the panoply of modulators and cell type-specific distribution of ERs results in an extended variety of possible effects, making widely variable the action of estrogens, in order to send specific signals to organs or groups of cells within a wide array of possibilities[92-95]. The ERs are, perhaps one of the best examples of receptor adjustment to the needs of tissues under varying conditions, attained through a considerable number of mechanisms. Both ER α and ER β are dimeric and coded by different genes[96,97], with an additional abundance of polymorphisms[98,99]. Their distribution in the cells of different tissues and organs is independent for each receptor[100], as are their final gene expression effects[101,102]. They can show synergic[103] or antagonistic[104] effects, even for the same molecular species, and depend, largely, on the post-binding relationships of the E2-ER complex. This situation is further complicated by the interaction of the ER (or E2-ER) with a number of different mechanisms of modulation, such as selective estrogen receptor modulators (SERM)[105-107]; selective ER down-regulators (or degraders)[108]; and the specific ERE, which directly affect the function of ERs[109,110]. Other closely related ("orphan" up to recently) receptors participate in the regulation of critical pathways, but in many cases their relationship with the ERs remains unclear.

Membrane estrogen receptors

In addition to the canonic nuclear ERs, estrogens also bind cell surface ERs[111-113]. As usual with ERs, the terms used to define these receptors shift between the importance given to their location, partial signaling pathway, speed of action and other considerations: membrane ER[114], non-nuclear/non-transcriptional signaling ER[115,116] non-genomic signaling ER; membrane-linked ER α [117,118] or both ER α and ER β [112]; caveolae- or lipid-related ER[119,120]; G-protein-coupled ER (GPER)[121,122]. This list adds to the existence of alternative or non-genomic "direct" or "rapid" effects of ER stimulation in some cells, eliciting immediate responses (a shift-or development-from the main advantage of the delayed steroid hormone signaling)[123,124].

All these effects suggest that, the ER structure is essentially that described above, with two main types (families) of complete/incomplete ERs: ER α and ER β , which are found in the cytosol (and nuclei) of cells, including members of the ER α family linked to G-proteins (GPRA1/GPR30)[122,125] attached or close to the plasma membrane.

The proven relationship of ER α to membrane or fat droplet-related structures may be a consequence of the adaptability of ER α [120]; the existence of free and fatty acid-esterified estrogen in lipid-related cell structures[126], or both. In any case, the association of ER α to caveolin-1[119] and then complexed with G-proteins, helps explain the presence-binding of the ER[127], and then E2 in the membrane entourage[128]. In this case, the signal may be transferred to membrane-related structures, as is the case with increasing calcium release[115]. The G protein-ER complex, upon the binding of E2 may also induce nuclear effects *via* activation of tyrosine kinases[129] and the MAP/ERK or PI3 α /Akt pathways[130]. The stimulated G protein-activated receptor may also signal through GPR30[131]. The activated system containing the ER also enhances adenylate cyclase activity[132] *via* phosphorylation of the cAMP response element[133]. However, these direct membrane-related mechanisms may

coexist with also faster direct translational actions of conventional ERs somewhat linked to membranes[134] or with other mechanisms hinted at but not fully disclosed yet[135,136]. This includes the presence of ER receptors within cell structures, such as mitochondria (*e.g.* ER β)[137].

It has been established that non-genomic effects of ER bound to E2 may belong to two confluent mechanism types: direct effects elicited from the membrane and effects developed through cytosol signaling cascades and actions. Both processes are probably coincident for different cell settings. Hypothalamic inhibition of guanylate cyclase[138] and LH secretion[139], as well as increased cell migration[140] and other brain effects[141] add to the widening array of non-genomic effects of ERs. Most of these effects have lately been attributed to the ER α irrespective of the place of binding with E2, but the implication of ER β has also been described[142,143].

Notwithstanding, all these receptor-related mechanisms described cannot fully explain all the biochemical effects induced by estrogen signaling[144-148], leaving ample space for the assumption of direct, *i.e.* non ER-related, involvement (largely of E2 and its C17-fatty esters, AE2)[149,150]. However, these effects have been described only in lipoproteins, other lipid masses or lipid/protein interfaces[54,151]. The direct effects of estrogens on mitochondria have been related to specific mitochondria receptors[152,153], apparently containing ER α , ER β [154] and other possible binding structures[155]. Their role on mitochondrial function, however, has been found to be significant[154,156], especially in the regulation of energy providing pathways[157, 158]. The possibility of estrogen direct incrustation in the lipid layer of membranes has been proposed as a way to modify their functionality[159] and enhance the E2/AE2 anti-oxidative properties in a way similar to its postulated function in lipoproteins[160, 161].

Estrone and AE1

E1 is a rather peculiar and resilient hormone (Box 4); we do not yet have a direct explanation for its massive synthesis and storage, since the lipophilic nature of E1 (but not that of SE1) limits its action in plasma, cell and interstitial space. Non-esterified E1 levels are related to those of E2, with E2/E1 ratios fairly stable for men (*c.* 1) and more variable for women (*c.* 1.5-2) up to menopause[162]. However, measurement of circulating estrogen is difficult, often showing poor correlations between instrumental and immunoassay results[163]. The relationship of E1 with E2 levels, in addition to sex (and age) is affected by diabetes/obesity[164]. Furthermore, analyses of SE1 seldom include other E1 esters nor free E1, which compartmentation (important in lipoproteins) skews E1 serum levels towards lower values. The obese show high plasma SE1 concentrations[165]. In any case, the whole-body AE1 content in rats is several orders of magnitude higher than free (and sulfate-esterified) E2[44], however, the AE1 content in obese rats is relatively lower than in normal-weight animals, despite AE1 being essentially stored in WAT[44].

The oral pharmacological administration of oleoyl-E1 to normal weight and obese rats[166,167], induces a marked decrease in fat depots[168], not dependent on the degree of obesity and diet[167,169]. The loss of fat runs parallel to the normalization of glycemia, blood lipids and other metabolic syndrome (MS) markers[170], without apparent effects of estrogenization, and irrespective of energy intake manipulation [171]. AE1 has been proposed as a ponderostat signal[170], since the excess fat is shed without accompanying metabolic disorders[170,172]. Its negative effects on humans are negligible (clinical studies, phase I, unpublished data), and the positive (*i.e.* loss of excess fat, lowered insulin resistance, absence of estrogenization) were outstanding in a single case published[172]. However, its development as a drug was abandoned because an ill-designed phase II failed to be conclusive. We have no hints as to the mechanism of AE1 signaling, other than it is synthesized in cultured adipocytes[50], and WAT stores these esters in large amounts[44,65]. AE1 treatment reduces the size of WAT lipid depots[173,174]. Natural AE1 is transported in the lipid fraction (lipoproteins) of blood[49,175]. Methodology is a critical factor for the analysis and tracing of acyl-estrogens, with disparate results; *i.e.*, it has been reported that human plasma does not contain AE1 at all[176].

The main effects of AE1 are a consequence of the structural change on the whole ester, not through the release of E1[177]. When injected, marked estrogenic effects are observed, with increased E1 and E2 levels[178]. However, oral administration of AE1 does not elicit the same signs of estrogenization[171]. A highly critical analysis of oleoyl-E1 actions on rat body weight found no significant negative effects[179]. Body protein and N balance are preserved in AE1-treated (lean and obese) rats[166,167,174, 180]. There is very little information available on AE1 mechanism of action. The structure of the orally administered ester seems to be modified, with low levels in

blood plasma[49,181,182], but an unidentified derivative is present in large concentrations, maintaining the estrogen nucleus in a more hydrophilic form[181]. In liver, AE1 label can be found linked to DNA shortly after administration[181]; the effects of AE1 imply the stimulation of ER α [183,184]. Excess AE1 is essentially excreted as SE1[185].

There are sufficient elements to sustain the implication of AE1 in the regulation of body weight[170], but the lack of further complete studies on its mechanism of action has prevented both its clarification and its eventual therapeutic application. No other explanation has been put forward to justify the limited estrogenic potency of E1, despite its massive synthesis in the ovary and the brain[186], and, especially (in quantitative terms) in WAT[187], with a direct relationship of its total body content and circulating levels with WAT, lowered by obesity in rodents and humans[47]. The effect of the administration of free E1 to rats induce some estrogenic effects and slightly increases body weight, effects quite different to those of its acyl derivative[177].

Estrogens and the regulation of energy metabolism

Glucose is the main energy substrate, and the main simple nutrient of human diet. Glucose is also the primary inter-organ energy substrate carried by the blood to sustain the energy needs of body cells. Carbohydrates capable of yielding glucose (or other interconvertible hexoses) are a necessary part of our diet[188,189], and for many thousands of years they have constituted the main staple of our energy intake. This role has been already addressed in depth in a previous paper[189] in which we discussed the final fate of dietary carbohydrate, protein and lipids to yield two- and three-carbon metabolites (2C, 3C) and anaplerotic four- and five-carbon (4C, 5C) molecules from proteins (when excess N could be disposed of). The common shared groups of metabolites from dietary nutrients include 2C fragments (and a smaller amount of 3C from glycerol) from fats and, essentially 3C fragments from the six-carbon (6C) hexoses. The 3C could be largely used to maintain glycemia thanks to hepatic[190], renal[191] and intestinal[192] gluconeogenesis, or simply used (pyruvate) as a source of 2C (to yield acetyl-CoA), which is largely oxidized to CO₂ in the mitochondria through the Krebs cycle. Most of the energy drawn from glucose is obtained from the pyruvate-lactate produced in the glycolytic pathway followed by the complete oxidation of pyruvate, as acetyl-CoA, in the Krebs cycle. The 3C fragments (essentially lactate, pyruvate, glycerol, alanine and serine) can substitute glucose as an energy substrate in many tissues, avoiding the strict control of glucose levels, and providing faster access to their energy when and if enough oxidative capability and oxygen are available[193,194]. Glucose isoforms often delay somehow the oxidation of glucose[195], and thus, the direct cell use of glucose-derived 3C fragments may speed up its catabolism. This C6→C3 massive conversion is one of the most important albeit less publicized functions of WAT[196]. The presence of excess lipids (and energy) in the diet often results in an excess of 2C fragments (mainly the result of catabolic oxidation of their polymers: fatty acids) that their oxidation becomes problematic, thus the excess of energy available facilitates their storage (often long term) as fats[189].

The inadequacy of diet composition, and especially the excess of energy from fats and carbohydrate results in the progressive metabolic disorders of MS[197] with the development of sustained hyperglycemia[198], often deriving into type 2 diabetes[199], obesity[200], altered blood lipids, with hyperlipidemia[201], deriving in endothelial inflammation[202,203] and increased cardiovascular risk[204], hepatic steatosis[205], depression[206], and increasingly functional alteration of the nervous system[207], bone[208] and practically all organ/cell systems, extended even to the microbiota[197]; and, essentially, the immune system[209,210]. The causes and effects of MS have been intensively and extensively studied, and a direct relationship has been found with diet composition and excess energy[211,212], but no effective solutions have been put forward. Medical treatment is commonly limited to increased energy expenditure and changes in type of food, and (decreased) energy intake[213-215], in most of the cases, without sufficient metabolic analyses[216]. This is complemented by the pharmacological treatment of the disorders included in the MS. The relative acceleration of the MS effects with age is more clearly observed in adult (and aging) men than in women[217,218]. This difference has been attributed to the obvious diet-driven inflammation of MS[219,220], compounded in men by the progressive decrease in the synthesis (and effects) of T, in part a consequence of aging but also by the hypoandrogenism that characterizes MS[221]. Women, from adolescence to the beginning of menopause maintain their high levels of E2 and functional hypothalamus-hypophysis-gonadal axis[62]. Menopause, aging and other causes

break this equilibrium and the levels and protective effect of estrogens wane; The E1 vs E2 ratio of concentrations is maintained at E2 > E1 in premenopausal adult women, changing to E1 > E2 in post-menopausal women and in men (in which there is little change with age). In both cases, E2 levels were lower in men and post-menopausal women than in adult premenopausal women[62].

In aging men, especially those with MS, treatment with T reduces to some extent cardiovascular risk[222,223] and helps maintain glycemia[224,225], but possible dangers, insufficient knowledge and scant physiological analysis have limited the extension of this therapeutic avenue[226]. Similarly, for women, substitutive estrogenization is partly effective[227-229] at menopause, but its extension has been seriously limited by the fear of possible negative consequences, as discussed in Box 1. In addition, synthetic estrogens are the most used substitute drugs despite our very limited knowledge[230] of the intricacies of their action in such complex mechanisms as those described above for E2. The case of tamoxifen (agonist/antagonist) is a clear example[231]. This generalized (albeit undeclared) ban on sex hormones extends to the use of T in women, despite the fact that both E2 and T are needed for bone[70,232] health, and T for body protein maintenance[75]. Obviously there are problems to solve, but it seems that this line of study has not been sufficiently developed for reasons not based on contrasted arguments. In the case of AE1, a line of research developed by only one research group, obtained better results than those of any previous anti-obesity drug[170,179], but the development was discontinued largely for fear of “possible” future negative findings[179].

Estrogens, insulin and dietary nutrients handling

Most of the studies on the effects of estrogen on glucose metabolism have been done using E2 (and other ER ligands). There is a very limited amount of specific information on E1 direct effects; however, SE1 was found to induce hypoglycemia in genetically obese mice *via* glucose-6-phosphatase[233]. The effects of estrogens on glucose and energy handling are mediated through four coordinated actions: (1) Protection and facilitation of insulin secretion and function in the control of glucose availability to tissues; (2) Modulation of energy partition, favoring the use of lipid as the main energy substrate when their availability is higher than that of carbohydrates; (3) Functional protection through antioxidant mechanisms; and (4) Central effects on whole body energy metabolism and homeostasis maintenance.

Estrogens, insulin and glucose

E2 protects the functionality of the pancreatic β cells[234,235], preventing apoptosis[236], adapting their function to insulin resistance[237], and maintaining their insulin content[238]. ER stimulation inhibits lipogenesis in the β cells[158], which limits the negative effects of excess lipid in the cell. The loss of the ER (nuclear and/or membrane) impairs pancreatic insulin secretion[239], which is stimulated by estrogenic signaling[240]. The lack of E2 availability also increases hepatic insulin clearance[241].

Estrogens also prevent the development of diet-induced insulin resistance[242]. The gender-dependent effects of estrogen on high-fat diet-induced insulin resistance are largely dependent on the anti-inflammatory effects of the hormone[243]. E2 increases tissue insulin sensitivity[244], and lowers insulin resistance in peripheral tissues[245], with marked differences in the effects depending on gender[243]. In female mouse adipocytes, E2 lowers inflammation (and thus insulin resistance[246]), and enhances the effects of insulin on tissues[247]. The sole activation of ER α AF-1 is enough to prevent obesity, liver steatosis and insulin resistance in mice[248]. However, obesity and insulin resistance seems to require E2 in addition to ER α and AF-2, AF1 not being essential[249].

Estrogens induce a considerable number of actions in the brain, which is also able to synthesize them[250], playing an important role in its function[251,252] and behavior[253]. E2 also interacts with serotonin to affect insulin resistance[254]. Estrogenic deprivation induces mitochondrial dysfunctions in the brain which may induce the loss of cognitive functions[255]. More complex is the long saga of the relationship of estrogen in the peculiar placing of brain insulin resistance in Alzheimer's disease[256, 257]. The neuroprotective actions of estrogens[258], added to the inhibition by E2 of β -amyloid production[259] and the implication of E2 in the regulation of insulin degradation in the brain[260], suggest an overall beneficial effect of estrogen limiting the development of this disease. However, Alzheimer's disease affects more women than men[261], and a number of caveats have been raised against the danger of natural estrogens being implicated in its development[262]. Right now the case is not solved, with studies showing a protective effect of ER β [263] and others hinting at the

implication of ER α in its pathology[264].

Estrogens, largely E2, facilitate the uptake of glucose from the intestine[265], and its extraction from the bloodstream by activation of transporters GLUT4[266] and, at least in the brain[267] GLUT1. E2 lowers liver glucose output with no changes in glycogen during mild exercise[268], a difference due in part to a modulable maintenance/inhibition of gluconeogenesis[269]. E2 also regulates glycolysis in endothelial cells by non-genomic pathways[270], partly by increasing insulin signaling[271]. Glucose catabolism is affected by estrogens, which stimulate glycolysis *via* phosphofructokinase[272], and the pentose phosphate pathway *via* Akt[273]. In any case, the direct incidence of ER signaling on glucose handling is relatively limited and conducted *via* modulation of insulin[271]. Probably, the main effect of estrogen may be the utilization of lipids as alternative energy substrates. This is important for humans, because of the common occurrence of excess lipids (and energy) in Westernized diets, which leads to problems in dietary substrate partition[189] and the common development of MS.

Lipid handling and estrogens

Estradiol: Estrogens lower circulating triacylglycerols (TAG) favoring their transport with a higher expression of ApoA5[274], and protecting lipoproteins against oxidation [275]. However, the main effect of E2 on lipids is favoring the shift from lipid deposition (storage) to its oxidation as energy substrate. Perhaps this is the most critical effect of estrogens on energy partition.

Treatment with E2 decreases obesity[276], protects against hepatic steatosis[277], lowers the activity of cholesterol acyl-transferase[278] and limits fat deposition[279]. All these are –again– indirect actions aimed to decrease the storage of excess TAG, since E2 does not directly regulate lipolysis[280]. Nevertheless, estrogens decrease lipogenesis[281] in WAT; and adipogenesis is also inhibited through ER α activation [282].

Dietary composition directly affects the substrate partition and the regulation of substrate utilization to maintain both energy and nutrients homeostasis[283]; in rats, hyperlipidic diets induce increases in E2 levels, and are correlated with an increased use of fatty acids as energy substrate[284]. The decrease in lipogenesis/adipogenesis (and the relatively enhanced lipolysis) frees the use of excess glucose and glycolytic 3C towards 2C and its oxidation in mitochondria; thus, decreasing the synthesis and storage of fatty acids (and TAG).

The effects of E2 on lipid handling are coordinated with the actions of E2 on insulin [235,285], glycemia[286] and the use of glucose as the direct energy substrate[271] instead of using it to fuel the synthesis of fatty acids. E2 lowers insulin resistance and fat storage through the ER α and the FA2 binding site[249]. Estrogens also lower the insulin resistance induced by excess dietary lipids[245].

A key point of these E2-derived metabolic shifts lies on the mitochondria[287,288]. Estrogen controls mitochondrial biogenesis and function[289]. E2 deprivation induce mitochondrial dysfunction and insulin resistance, which may induce alterations in the cognitive ability of subjects[255]. E2 potentiates the oxidative capacity of mitochondria, through increases in cAMP and cytochrome C oxidase activity[290]. E2 also inhibits the synthesis of adenosine triphosphate (ATP) in the mitochondria[291], which may be related to the increase in oxygen consumption and energy expenditure elicited by E2 [292], and its postulated role enhancing heat production and thermogenesis[293,294], which imply a higher overall substrate oxidative activity.

The pyruvate dehydrogenase complex (PDH) is a critical control node, which catalyzes the irreversible conversion of 3C pyruvate to 2C acetyl-CoA in the mitochondrion. The main mechanism of PDH control is phosphorylation, mainly by (inhibiting) PDH kinase 4 (PDHK4)[295]. Insulin inhibits the expression of PDHK4 [296], which has an increased activity during starvation and diabetes[297]. The levels of PPAR γ coactivator-1 α (PGC-1), an important cell energy regulator[298,299], which is also increased during diabetes and starvation, modulates the function of ERs[300]. PGC-1 increases hepatic gluconeogenesis through the expression of phosphoenolpyruvate-carboxykinase[301], and co-activates, with estrogen-related receptor (ERR), the expression of glucokinase[302]. PGC-1 increases the expression of PDHK4 [303], essentially through the activation of ERR (mainly the ERR α and ERR γ isoforms) [304]. ERRs are homologous to the nuclear ERs, but they are orphan receptors, *i.e.* do not have specific ligands such as E2[305]. Recently, it has been suggested that PGC-1 could be considered, perhaps, their unique non-steroid ligand[306]. ERRs increase glycolysis and glucose uptake[307].

The activation of PDHK4 by ERRs and PGC-1 is inhibited by insulin[303]. However, E2 activates ERRs[308]. In sum: insulin activates PDH, which is inhibited by ERRs modulated by cell lipid energy conditions (PCG-1) in a way that facilitates a decrease

in insulin resistance[309] and a steady flow of 3C to 2C into the mitochondria to fuel the Krebs cycle, since lipogenesis is inhibited[281,310] and cannot absorb the newly formed acetyl-CoA.

Further stimulation of mitochondrial oxidative capacity[153,311], and the availability of 4C and 5C derived from amino acids, further speeds up the oxidation of 2C by the mitochondria of liver, WAT and specific brain sites[312]. The accessibility of amino acid hydrocarbon skeletons depends on their increased oxidation (when in excess and limited capacity of the Krebs cycle[189]) *via* the alternative oxidation of amino groups to nitrogen gas[222,313]. The presence of these anaplerotic fragments and the higher oxidative capacity markedly increase the use of acetyl-CoA (from fatty acids or glucose) as the main energy substrate. The added relative inefficiency in the production of ATP[291] further helps the estrogen-controlled metabolism of adult women to dispose (albeit partially) of unwanted excess dietary energy. This effect may account in part for the resistance of women to develop the MS in its double facet of obesity and diabetes[314].

Estrone and acyl-estrone

E1 has not generated as much literature as E2, but this is probably a consequence of its limited direct effects on classical estrogenicity and energy metabolism. However, it has been found that SE1 also contributes to glucose homeostasis, inhibiting glucose-6 phosphatase under conditions of hyperglycemia[233]. SE1 also lowers the levels of lipoproteins in postmenopausal women[315]. And, obviously shows estrogenic effects when given in pharmacological doses, albeit less marked than those of E2.

The anti-obesity effects of oleoyl-estrone, an AE1 ester, were studied extensively for a short time[170], but ceased before the appearance of many key studies on estrogen function and mechanism of action cited above. Thus, these older studies have to be re-analyzed from the present-day perspective. The acyl moiety of AE1 comparatively affects only partially its slimming effects[48], thus, oleic acid (the most abundant in the rat body stores) was used as standard. The E1 moiety, surprisingly, is not essential either, since both AE2 (at pharmacological levels) and oleoyl-diethyl-stilbestrol show marked body fat slimming effects[48]; however, these compounds have not been studied further because of the marked estrogenic response (toxic at the pharmacological levels analyzed) they elicited in comparison with AE1 or even E1 alone.

AE1 is not estrogenic[171]. However, the injection of liposomes loaded with AE1 induces estrogenic effects in rats due to the large amount of E1 produced by its hydrolysis[178]. The oral administration of AE1 basically excludes most of the E1[316] formed in the intestinal hydrolysis of AE1. In any case, SE1 is, finally, the main catabolite of AE1[185] (and of E1), since the fatty moiety poses no problems to its complete oxidation. This way, the interference of estrogenic effects has been circumvented simply by oral (instead of *i.v.*) administration of AE1, allowing a more direct analysis of its effects on body lipids[167,169,173]. The administration of AE1 preserves body protein[167,169,317], but markedly decreases body fat through the maintenance of a negative energy balance[167,169,177,180,317]. The process is achieved by lower food intake and unchanged thermogenesis[180] (an effect partly shared by E2 but not by E1), as well as a shift in the management of dietary fat, from accrual to oxidation for energy[88,318], such as described for E2. The effects of additional reduction of food availability are comparable (and additive) to those due to decreased appetite elicited by AE1[317]. Circulating levels of AE1 are proportional to body fat[65,182]. However, obese rats have lower AE1 levels than their lean counterparts[44]. In sum, the main effect of AE1 (given at pharmacological levels) is to shed excess body fat, without additional metabolic interference[174]. AE1 circulating levels presumably act as an indicator of whole body fat reserves under normal (not MS) conditions[319]. The AE1-induced loss of body TAG implies the concordance (described for E2) of peripheral (especially WAT) lipolysis[320], decreased lipogenesis[321] and higher energy expenditure and lipid oxidation[318].

The effects of AE1 on glucose metabolism are comparable to those described for E2: regularize hyperglycemia[174], decrease insulin resistance[174] and an overall antidiabetic action[322]. However, these effects may be just the consequence of the normalization of energy homeostasis induced by pharmacological doses of AE1[170], with full activation of the estrogen shift explained above: increased mitochondrial oxidation of 2C (and excess 3C) instead of storage of excess 2C mainly in the form of TAG-fatty acids.

The similarities of AE1 with E2 are both quantitative and qualitative. The well-known summarization of E2 function as less estrogenic than neuroprotective[323] is not applicable to the comparison with AE1 because these esters do not show either of these functions. Nevertheless, injected AE1 label has been found in cell nuclei[181],

and AE1 binds the ER α [183,184], but E2 cannot displace AE1 from its binding[171]. In addition, the pharmacological effects of E2 and AE1 are not superimposable[177]. This is compounded by the lack of full inhibition of AE1 actions on rodents by tamoxifen [324] and fulvestrant[184] (in fact, tamoxifen mimicked some of the effects of AE1[324]). These data help finally differentiate the effects of AE1 from both E1 and E2, and suggest that AE1 is, probably a SERM.

Functional protection through antioxidant mechanisms

E2 and E3 (but not E1) are considered effective antioxidants[325], since they help protect structural lipids from free radicals[326]. The polarized structure of estrogens makes them ideally suited to interact in interfaces between hydrophilic and lipophilic media[327], such as membranes, including mitochondria[160]. In this aspect, perhaps the AE2 esters may be the most effective, because in addition to E2, their most common acyl moiety, linoleic acid[328], is itself a main component of membranes [329], albeit being easily oxidized by free radicals[330]. The AE2 have been described as powerful antioxidants, more effective than free E2[331]. This role includes mitochondria, closely related to estrogen action for increased numbers, oxidative capacity, metabolic function and survival[161]. In this sense, both E2 and AE2 (and, probably to a lesser extent E1), control[332] and protect mitochondria in brain, liver and other tissues[156,161,333]. The antioxidant effects of estrogens seem unrelated to the classical estrogenic activity[334].

The AE2 antioxidant function is not limited to membranes, since their presence in lipoproteins helps protect them from scavenger radicals[275], maintaining their transport and signaling function. Since acylation on C17 of E2 results in a more effective antioxidant molecular type[55], and no other estrogens seem to specifically carry out this task, its uniqueness, and the importance of the function suggests that the AE2 may constitute, by themselves, a different specialized type of estrogens carrying out a critical and specific function for which they are best suited.

Whilst AE1 do not show significant estrogenicity[171], AE2 are markedly estrogenic [126,150,244], and maintain this estrogenicity longer than the 3-acyl-E2 esters[150], which suggests that they may-precisely-retain this property when packed in lipoproteins, such as low density lipoprotein (LDL)[126] or bound to plasma proteins [335]. When taken together, these properties suggest that the AE2 may, at least, fulfill the role of transport/storage of E2 in addition to an antioxidant function.

Central-mediated effects of estrogens on energy homeostasis

The main arguments for the postulated subdivision of estrogens in four separate classes, based on their structure and function is based on widely different availability of sources, but the marked differences observed suggest -at least- the existence of four groups, described in Table 1, which summarize most of the information provided in the present study.

E1:

Structural: Estrin nucleus, with only one phenolic-OH.

Functional: Mild estrogenic effect; a main precursor in the synthesis of E2; main catabolite in the excretion of estrogens as SE1; SE1 being probably the main signaling form of E1; increases growth during development; quantitatively the most abundant molecule with an estrogen nucleus in the body; possible “reserve” for rapid conversion to E2 or AE1.

Targets: (Generalized); WAT; reproductive-system organs.

AE1:

Structural: Estrin nucleus, with only the phenolic-OH esterified by a fatty acid.

Functional: No estrogenic effects; product of esterification (or interchange) of E1, probable active SERM for ER α , activates lipid catabolism, *via* lipolysis and oxidation of fatty acids; postulated as ponderostat signal, markedly lowers body fat; maintains glycemia.

Targets: WAT; brain; liver.

E2:

Structural: Estrin nucleus, with the phenolic-OH, and another-OH in C17.

Functional: Main estrogen; marked classical estrogenic effects, protects insulin and facilitates its secretion, maintains glycemia; indirectly activates lipolysis and inhibits lipogenesis; protects and favors the increase and oxidative function of mitochondria, lowers body fat, has antioxidant capability.

Targets: Brain, liver, mitochondria, reproductive-system organs, bone.

AE2:

Table 1 Comparison of the effects/functions between the main functional types of estrogens¹

Effect/ function/ action/ characteristic	E1	AE1	E2	AE2
Bind the ERs at the hormone binding site	↑↑ ²	X	↑↑ ²	~
Bind the AF1 or AF2 sites of the ERs	X ²	↑	X ²	~
Bind to mitochondria (and some membranes)	~	~	↑ ²	↑ ²
Elicit a direct classic estrogenic response	↑ ²	X	↑↑ ²	↑↑ ²
Induces hypoglycemic effects	~i	↑↑ ²	↑ ²	~
Is carried by lipoproteins	↑ ²	↑↑ ²	X	↑ ²
Show anti-oxidative effects	~	~	↑ ²	↑↑ ²
Activate the 3C→2C conversion (pyruvate dehydrogenase)	~	↑2	↑↑ ²	~
Increase mitochondrial oxidative activity	~	~	↑	~
Increase whole body thermogenesis	~	↑ ²	↑ ²	~
Show lipolytic effects	X	↑	↔	~
Show lipogenic effects	↑	↓ ²	↓ ²	~
Decrease WAT fat mass/ limits fat deposition	↓	↑↑ ²	↑ ²	~
Allow the activation of the alternative N disposal pathway	~	~	↑	~
Decrease body protein mass	↔	X ²	X ²	~

¹Specific early development and pregnancy-related estrogen molecular species and functions not included.

²Shows a coincidence of effect/function for different estrogen types in the same row.

↑: Exerts the effect described; ↓: Exerts an effect opposite to that described; ↔: Variable/not univocal responses; X: Does not exert the effect described; ~: Absent or insufficient information available; E1: Estrone; AE1: Acyl-estrone; E2: 17β-estradiol; AE2: Acyl-E2; ERs: Estrogen receptors; AF1: Activation function site 1 of the estrogen receptors; AF2: Activation function site 2 of the estrogen receptors; WAT: White adipose tissue.

Structural: Estrin nucleus, with only the phenolic-OH, esterified in C17 by a fatty acid, often polyunsaturated.

Functional: The most effective estrogen form of antioxidant; postulated as an element of transport or reserve of E2, protects lipoproteins, membranes and cell components, marked estrogenic action.

Targets: Mitochondria; plasma lipoproteins.

This partial (and incomplete) classification of the main estrogens is based on both structural and functional aspects. The estimated quantitative mass of these four types of estrogen (under standard conditions) in the whole body is: AE1 > E1 > E2 > AE2.

Estrogen is a fundamental modulator of female functions (including estrogenicity *stricto sensu*), which agrees with the high levels of E2 in adult pre-menopausal women. No sufficient data are available to show other gender differences in the postulated groups of estrogens, except for AE1, which pharmacological effects in obese rats are more intense in males than in females.

Estrogens, essentially E2, are responsible for the development of the sex-dependent structures (both physiological and psychological) related with mating and reproduction. Evidently this is achieved with the collaboration of other hormones, *e.g.* androgens, progestogens and peptidic hormones. It is unclear whether the other three groups of estrogens depicted in Table 1 play a specific significant role in the reproductive processes (with the exception, perhaps, of AE2).

The other key places for action of estrogens are characterized by containing ERs and are found throughout the whole body[336]; but WAT[337], liver[338], muscle[339], and, essentially the brain[340,341] are the main targets for their actions, and are, at least, the best studied. ERβ globally regulates lipid homeostasis[145], its activation in obesity increases whole body metabolism and mitochondrial biogenesis as a counter-measure to excess WAT lipid storage[312]. Oophorectomy alters WAT lipid metabolism[342], the plasma levels of E2 are affected by diet[284] and determine body fat deposition[343], probably through central (brain) control mechanisms.

In the hypothalamus, where E2 interaction with serotonin has been described[254]. E2 regulates sympathetic nervous control[344]. E2 and AE1 have marked anorectic

effects[180,345]. The postulated ponderostat effect of AE1[181,319] depends on its action on brain, where blood-injected label has been found[181]. The effects of estrogens on glucose and body fat have been attributed to central actions on the brain [15,346]. This is a logical assumption, including also T[347], because the brain controls the body energy metabolism[16] and homeostasis[348], *i.e.* regulates the coordinated biological maintenance systems of the body[349,350].

General considerations and conclusions

The growing number of known actions of estrogens in metabolic control cannot be fully explained by only the analysis of the “common” estrogens, essentially E1, E2 and E3 (with their sulfates). Thus, acyl-estrogen derivatives have also been included: Despite being known for a long time, and used in pharmacology, they are seldom included in general analyses of estrogens. These compounds are quite diverse. However, in practice, the studies available are limited only to acyl esters of E1 (on C3) or E2 (largely on C17); their properties are quite different, starting with estrogenicity, and continuing on to antioxidant or lipid wasting effects (Table 1).

In any case, the differences in effects induced by E1 and E2 (those of E3 seem to be closer to E2), are considerable, both in their classical estrogenic power and in their implication in regulative mechanisms: E2 being more powerful than E1 in almost any aspect related to metabolic regulation, becoming the most representative estrogen. Nevertheless, a large proportion of E2 is synthesized from E1 by widely distributed 17 OH-steroid dehydrogenases[351]. The similarities between E1 and AE1 actions are small, the latter resembling more E2 in its metabolic effects, than E2 *vs* AE2, despite the strong relationships in the main functions of AE2: antioxidant and estrogenic.

Due to the crossed coincidences of effects between E1-E2 and their acyl esters, a loose classification based on functions and structure has been developed and presented here. Either separately or as a conjoint “estrogens” block they may provide a comprehensive explanation of most of the actions of estrogens, which could not be attributed in any way solely to either one or to all the usual non-esterified estrogens as a group. It is also remarkable that these four groups constitute, together, an extensive fully synergic unit of action: antioxidant effects protect mitochondria, membranes and lipids, which are actively used for energy, limiting insulin resistance. However, the protection extends to insulin (and the pancreatic β cells); insulin secretion is maintained to sustain a steady glycemic response. Glucose is converted to 2C only when it is in excess, whilst dietary lipids (at the root of inflammation and development of MS) are not accrued but oxidized. Protein is preserved by strong, effective and well established mechanisms; but excess energy (and glucose) does not prevent the utilization of amino acids for energy, and, especially for efficient operation of the Krebs cycle thanks to the supply of 4C and 5C fragments. The problem of excess N disposal[189], strictly overprotected *via* the urea cycle is compensated using the direct pathway to produce N_2 [189]. Lipoproteins remain functional thanks to the steroidal antioxidants, TAG transport is practically unaltered, but lipogenesis is maintained low, and lipolysis high to dispose of excess 2C energy. Thermogenesis is maintained and appetite (and food intake) are adjusted to the real needs of energy intake (plus the use of unnecessary fat reserves). A happy metabolic Arcadia under the rule of essentially one (multiple) hormonal factor: estrogens.

Figure 2 shows the main interactions of simple estrogens (essentially E2) and AE1 on the core of intermediate energy metabolism, the meeting point of carbohydrate, lipid and protein catabolism. The antioxidant effects of AE2 (and E2) have been omitted, since their main point of action lies, just from the critical step 3C $\rightarrow$ 2C and the Krebs cycle, within the mitochondrion. The coordinated implication of estrogen types in the control of this segment of substrate handling is pervasive, both by direct implication and through its modulation of insulin action, and helps clarify that the implication of estrogens (as a whole) on glucose handling (and insulin control) is very high. The control node of energy metabolism lies in the mitochondria/cytoplasm interface, and-perhaps-critically on PDH. Around this point, directly linked to oxidative function of mitochondria and their generation of ATP, the implication of estrogens is high, as are the adjustment of the supply lines of 2C and 3C, the control of glycemia and the shift of amino acid catabolism under conditions of abundant energy (and glucose) availability[189].

In addition to the need to consider the estrogens as a group of several molecular species sharing a common biochemical structure and origin, implied web-like in a large number of coordinated metabolic functions, the main conclusion of this review is, precisely, the paramount metabolic importance of the estrogens. This is based on the synergy between the different forms of estrogen to maintain energy (including, obviously, glucose homeostasis), whilst preventing oxidative damage, lipid-induced

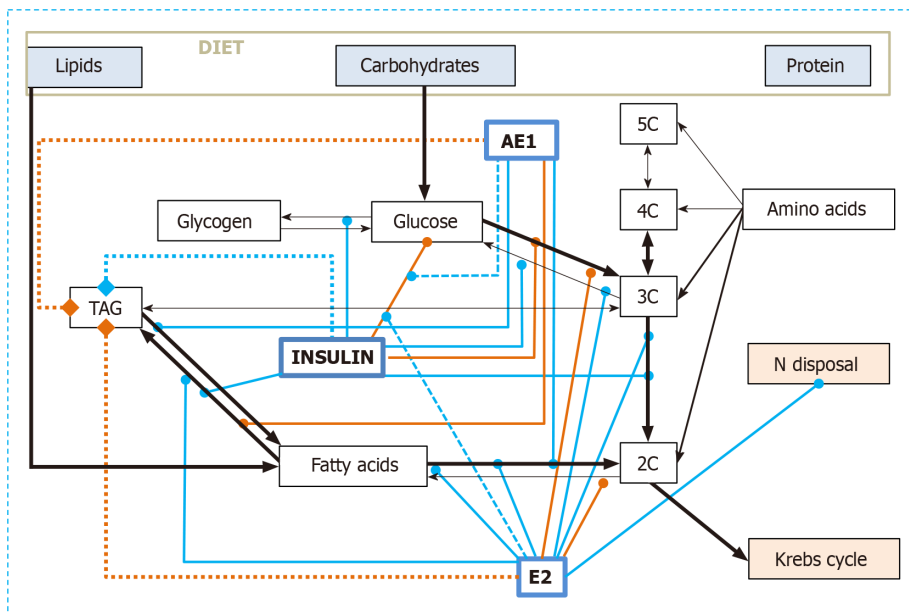


Figure 2 Combined regulatory effects on the utilization of dietary nutrients as energy substrates of insulin, 17 β -estradiol and acyl-estrone. Black arrows: Metabolic relationships; solid green lines: activation/enhancement; solid red lines: deactivation/inhibition. Dashed green lines show activation effects on regulatory processes. Thicker dot lines with final diamond symbols represent the enhancement (green) or decrement (red) of TAG reserves. For the sake of simplicity, other regulatory agents are not shown, and neither are their interactions. AE1: Acyl-estrone; E2: 17 β -estradiol and other E2-group estrogens

inflammation, excess fat accrual (and thus, obesity), and easing nitrogen excess normalization. This short (and incomplete) list is quite similar to a prescription for preventing the development of MS. Abundant epidemiological and limited experimental data support this assertion. It seems that we have to look more openly at estrogen forms to better understand their nature and properties, and to use them to fulfill their natural purpose as wardens of energy homeostasis (Box 5).

BOXES

Box 1 extended negative opinions on “sex hormones” hamper their investigative study and clinical development

In the case of “sex hormones” (*i.e.*, estrogens and androgens), the intensive pharmacological development has not displaced from use the most representative natural hormones: E2 and T from the front line of pharmacotherapy. However, the abuse of synthetic drugs (anabolic steroids, for instance) for purposes not strictly medical[352, 353] have clouded the relatively recent recovery of T as a critical hormone for energy-partition[354,355].

The widely extended negative opinion against “sex hormones” continues to seriously hinder the use of T in the treatment of aging- and MS-related hypogonadism in mature and old men[225,356]. The “opinion war” against estrogen is, currently, even harder to overcome, because of its direct implication on women’s sex; and because the social, political, and even religious arguments coalesced to raise questions (real or inflated[357]) against their use for any purpose outside a few restricted and socially-conditioned gynecologic disease applications[358-360]. The fact that the natural hormone E2 continues to be the main (and effective and cheap) estrogen standard drug only adds to the widely extended negative bias against estrogens[205, 361].

Box 2 critical methodological questions - the differences between species

Most of the problems caused by pharmacological overdosing of androgenic anabolic drugs or estrogens are probably secondary to blocking the hypothalamus-hypophysis-gonadal axis, a possibility observed many years ago[362], but seldom taken into consideration in clinical practice (and even less when the use is not medically justified). Because of this problem, continuous administration of excess anabolic androgens, can result in the loss of reproductive function[363] in addition to the derangement of their regulative metabolic (or/and psychological) functions.

Most of the metabolic studies on estrogens have been carried out in rodents for obvious reasons, but there are clear differences in the estrogen (and androgen) functions in rodents from those in humans. This includes a number of aspects, starting with the most obvious: size, metabolic rate and lifespan. The duration of the reproductive cycle, “estrus” or “heat” of rats and mice is shorter than the human ovarian cycle (which incorporates parts of the estrus cycle[364]), but their extension, phasing and physiological structure are different. The estrus is observed in most mammalian species (not in humans and apes), and is marked by changes in body temperature and energy expenditure[365]. Size affects energy expenditure (allometry) [366] and lifespan[367]. The fact that women are usually uniparous and rats normally have a two-digit number of pups (requiring a much higher energy and nutrient supply effort at the expense of the dam) is also a quantitative difference that makes uncertain the direct comparison of hormone changes and their timing, and of substrate dynamics, between different species and reproductive cycle models. Another key difference, explained above, is the E2 (and T) transport in plasma. Humans carry E2 and T bound to SHBG in high proportions of total circulating hormone, but SHBG is absent in mature rodents.

Box 3 steroid hormones as medium-term signals focused to control gene expression

Steroid hormones have longer circulating-lives than most other hormones (or other signaling molecules), which are rapidly produced (or released), then act and are inactivated, all in a short time-span. The maintenance along time of rapid-response signals is kept thanks to repeated secretion-activation/inactivation-destruction processes, which allow for rapid regulation changes, again in a short period of time. Steroid hormones, however, are produced and secreted to last for much longer periods; their prime mechanism of action is, essentially, gene translation, a process which requires more intensity of signal and longer stimulation periods. The advantage of steroids is their unbeatable stability over time in comparison to short term-effect peptidic hormones, catecholamines, *etc.* The target tissue specific needs are adjusted through the expression of different receptors and signaling pathways for the same steroid hormone, with additional modulation of expression, or by the numbers or proportions of molecular species, allowing for further modification of their effects under changing conditions.

Box 4 estrogen structural resilience and the environment

Estrogenic signaling is very ancient, affecting quite a number of phyla as observed by the use of estrogen analogs in the context of co-evolution of plant allopathic defense against herbivores[10,368]. The estrin nucleus is highly resistant to environmental oxidation or bacterial catabolism[369]. The non-biological disposal of human waste induces the accumulation of estrogens in continental waters[370] and its sediments [371]; they are also found in sea sediments[372]. Persistence of estrogen in the natural medium has another negative aspect, the environmental effects of waste estrogen [373], affecting both invertebrates and vertebrates[8]. Human and domestic animal overpopulation extends the increase of estrogenic waste problem to become a serious health, ecologic and economic[8,374] problem that should be understood and adequately addressed.

Box 5 perspectives: the need for further advance in our knowledge of estrogens

A critical point for the continued use of estrogens in medicine is that of the extended use of molecules designed for specific clinical applications[375]. All these patented molecules do mimic some aspects of physiological estrogen actions, but not all of them [375]. The synthesis of estradiol analogs has been oriented to increase only some effects, sought for specific clinical applications[9,376]. However, most of these compounds were designed before our knowledge of estrogen function, mechanisms of action and metabolic effects were fully known[377]. In fact, right now, our knowledge of the full list of estrogen effects is incomplete. For instance, the role of estrogens in the control of brain organization[378,379], adjustment of the immune response[380,381], or even the estrogen function in core energy metabolism regulation[15].

The proof of our limited knowledge is the lack of a clear picture of all the physiological actions carried out by estrogens. Thus, how can we expect to extend this needed knowledge to drugs devised with specific (not global) objectives? How to test their effects on functions that so far have not even been uncovered or analyzed in the classical estrogens? In fact a similar caveat should be applied to all other steroid hormones, especially corticosteroids and androgens.

We are aware that the binding modulation of the effects of estrogenic drugs is unclear, especially as to which real estrogen (as a whole) actions are carried out by each of these compounds[382,383]. In any case, during the last 70-90 years, the use of synthetic estrogens has been slowly substituted by natural estrogens[383,384], with the practical abandonment of the wonder drug diethylstilbestrol. The case of anabolic androgens (and testosterone itself) is paradigmatic: the continued use of these drugs results at least in infertility[385] and cardiovascular damage[386]. The continued use of estrogens, in particular powerful analogs, may result in unexpected, possibly negative or unexplained effects[384,387,388], simply not detected because the protean nature of estrogenic action has not permeated yet to clinical (and, especially, pharmacological) practice.

We are uncovering the proverbial tip of the iceberg of a group of steroid hormones; we need a deep analysis of estrogen functions, both from the molecular and regulatory aspects, but never forgetting that steroids act on the whole body not only on specific organs and single isolated pathways. The actual role of hormone carriers in plasma (*i.e.* SHBG), the cyclic hypothalamic-hypophysis-gonadal axis function, and the possible disorders induced by estrogenic drug substitutes, must be studied and adapted to human physiology in order to be able to resolve endocrine disorders as a whole. First: do no harm; the effects of estrogens and analog drugs under clinical conditions must be known and fully evaluated because not all estrogens and related drugs act the same way[383,384].

Last, but not least, the real and realistic implication of estrogens (as well as androgens and corticosteroids) in the regulation of the metabolic hub of energy partition should be clarified. This is an essential step to limit the ravages of aging and to understand (and correct) disorders such as the widely extended MS.

CONCLUSION

The main conclusion of this review is, precisely, the paramount metabolic importance of the estrogens. This is based on the synergy between the different forms of estrogen to maintain energy (including, obviously, glucose homeostasis), whilst preventing oxidative damage, lipid-induced inflammation, excess fat accrual (and thus, obesity), and easing nitrogen excess normalization.

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