MINIREVIEW

Steroids and Thermogenesis

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Summary

Apart from thyroid hormones, as the main hormonal regulators of obligatory thermogenesis, and catecholamines, as major hormonal regulators of facultative thermogenesis, production of heat in homeotherms can also be influenced by steroids. Generally, hormones can influence heat production by regulating the activity of various enzymes of oxidative metabolism, by modulating membrane protein carriers and other membrane or nuclear protein factors. Proton carriers in the inner mitochondrial membrane, known as uncoupling proteins, play the key role in heat dissipation to the detriment of the formation of energy-rich phosphates. In this minireview we have focused on the effects of steroids and thyroid hormones on heat production in brown adipose tissues and in skeletal muscles, with particular respect to their effect on uncoupling protein expression. Apart from hormonal steroids, dehydroepiandrosterone, an important precursor in the metabolic pathway leading to hormonal steroids which possess many, mostly beneficial effects on human health, modulates metabolic pathways which may lead to increased heat production. Recent studies demonstrate that 7-oxo-dehydroepiandrosterone, one of its 7-oxygenated metabolites, is even more effective than dehydroepiandrosterone. Recent findings of various actions of these steroids support the view that they may also participate in modulating thermogenic effects.

Introduction

The maintenance of a constant body temperature of homeotherms in a very narrow range, under different physiological conditions (e.g. temperature, physical activity, food intake), requires a sophisticated regulatory system both at the organ and cellular level. One of the thermoregulatory mechanisms, the non-shivering thermogenesis, can be divided into two categories: obligatory and facultative. The former is essential for the life of all cells of the body and can be defined as the basal metabolic rate (for review see Janský 1995). The most important endocrine factors modulating obligatory thermogenesis are thyroid hormones (Janský 1995, Lanni *et al.* 2003). Besides shivering, the facultative thermogenesis is regulated mainly by catecholamines released from adrenals and the sympathetic nervous system (Janský and Janský 2002). Obligatory thermogenesis proceeds continuously in all organs and tissues of the body, while facultative thermogenesis can

be rapidly switched on or off in response to the actual situation. It is produced mainly by two organs: brown adipose tissue (BAT) and skeletal muscles. In humans, in contrast to rodents and some other mammalian species (e.g. hibernating animals), the BAT thermogenesis is important only at birth and in early infancy. In adults the amount of heat produced by BAT is small.

Thermogenesis and uncoupling proteins

From a biochemical point of view, heat is a portion of energy liberated during oxidative phosphorylation through electron transport in the respiratory chain, within the mitochondrial matrix. The inner mitochondrial membrane, in contrast to the well permeable outer membrane, contains several transmembrane proteins serving as antiport systems for the exchange of anions between anion matrix, (as the site of transport of electrons and reducing equivalents). Out of these ADP-ATP- and phosphate transporters have significant amino acid homology with another group of transmembrane proteins that translocate H^+, known as uncoupling proteins (UCPs). Concerning heat production, the principle event is proton pumping by the respiratory chain and proton leak back to the matrix (Brand 1990). Generally, oxidative phosphorylation is driven by the electrochemical gradient across the inner mitochondrial membrane. In BAT UCP-1 serves as a unique alternative route of proton entry, through which protons bypass the ATP synthase route of entry and energy of the electrochemical gradient is dissipated as heat (Argyropoulos and Harper 2002). For a review of UCPs in humans see Langin et al. (1999) and in animals see Ricquier et al. (2000).

The mechanism of UCPs action was extensively studied in recent years and several excellent reviews addressing these topics are available (Klingenberg and Huang 1999, Garlid et al. 2000). In brief, two models were suggested, both emphasizing the role of fatty acids in proton translocation. According to Klingenberg (1999) UCPs conduct protons through a hydrophilic pathway lined with fatty acid anionic groups that buffer the protons as they move across the membrane. In other words, UCPs themselves serve as alternative proton channels. According to the model introduced by Ježek (1999) and Garlid et al. (2000), UCPs do not conduct protons, but they rather function as anion carriers, transferring fatty acid anions. As protonated fatty acid difuse freely across the membrane, UCPs translocate the fatty acid anions, thus enabling proton "cycling".

In this minireview, we will focus on the role of steroids and thyroid hormones in regulation of obligatory thermogenesis, with particular respect to UCPs functions.

The regulatory role of thyroid hormones

Basal metabolic rate reflects the activity of mitochondria and is coupled with the formation of high-energy bonds in ATP (Goodman 2003). Thyroid hormones are the major hormonal regulators of oxidative metabolic processes (Janský 1995, Lanni et al. 2003). Total oxidative metabolism at rest (basal metabolic rate) measured by oxygen consumption, is highly sensitive to thyroid status. Long-lasting clinical experience shows that patients with hypothyroidism are susceptible to cold, while an opposite effect is observed in hyperthyroid subjects. Generally, thyroid hormones regulate gene expression of various proteins – enzymes and other factors involved in oxidative metabolism through the interaction with intracellular receptors of the thyroid-steroid hormone superfamily. For instance, triiodo-thyronine accelerates ATP-dependent processes as demonstrated by the activation of sodium/potassium-ATPase (Goodman 2003) or Ca^{2+}-dependent ATPase from sarcoplasmic reticulum (Simonides et al 2001).

As early as in the fifties, a hypothesis was proposed that triiodothyronine (T_3) is responsible for uncoupling of electron transport from the synthesis of ATP (Lardy and Feldcott 1951). With respect to the key role of UCPs in facultative thermogenesis, the pertinent question comes up on the effect of thyroid hormones on the expression and function of UCPs. Recent studies on animal models demonstrated unequivocally that thyroid hormones induce UCP synthesis as early as at the mRNA level. For instance the Italian authors (de Lange et al. 2001, Goglia et al. 2002, Lanni et al. 2003) as well as others (Cunningham et al. 2003, Quiroz et al. 2004) reported sufficient evidence that thyroid hormones stimulated mRNA expression of UCP3 in rat skeletal muscles and the heart, and to a much lesser extent in spleen, lung or liver. Inhibitors of protein synthesis, e.g. actinomycin D, almost completely abolished this effect (Moreno et al. 1997). In these experiments, the onset of mRNA and the protein increase ran in parallel with the changes of oxygen consumption. It was also shown that UCP3 expression in skeletal muscles is due to a direct effect of T_3 rather than to β-adrenergic stimulation, since the effect of T_3 was not altered significantly by

β-adrenergic blockers (Quiroz *et al.* 2004). A further experimental tool has brought a development of a novel, highly sensitive peptide antibody to UCP3, which is discriminatory for UCP3 over UCP2, UCP1 and other mitochondrial transporters (Cunningham *et al.* 2003). This antibody detects UCP3 expressed in yeast and it can also detect human, mouse and rat forms of UCP3. Similar results as with muscles were obtained with cultured rat brown adipocytes (Hernadez and Obregon 2000). In the latter case T_3 dramatically increased the effect of adrenergic stimulation of thermogenesis. It was concluded that UCP3 is the molecular basis for the modulating effect of T_3 on thermogenesis.

In humans UCP expression depends on many factors like energy expenditure, diet and last but not least, it is under complex hormonal control (Langin *et al.* 1999). As only few reports deal with the thyroid hormone effect on UCP expression, indirect evidence prevails. For instance, Boivin *et al.* (2000) measured mRNA transcripts of two UCPs (2 and 3) in bioptic samples of adipose tissue and skeletal muscles from lean, healthy men. The amounts of mRNA were correlated with the resting metabolic rate and actual hormone levels (thyroid hormones, insulin, glucagon, leptin, catecholamines). All these factors contributed to a great variability of the resting metabolic rate, but no correlation was found between them and UCP (2 and 3) mRNA formed. Indirect evidence for increase of thermogenesis by mitochondrial energy uncoupling was presented by Lebon *et al.* (2001). The authors measured $^{13}C/^{31}P$ by nuclear magnetic resonance in mitochondria from skeletal muscles of healthy male volunteers before and after treatment with T_3. While ^{13}C moiety reflecting tricarboxylic acid cycle fluxes increased considerably, the rate of ATP synthesis remained unchanged. The direct effect of thyroid hormone treatment on UCP2 and UCP3 gene expression was studied in Pima Indians, who are a rewarding object for studies of obesity; T_3 increased expression of both transcripts (Schrauwen *et al.* 1999).

Thermogenesis and steroids

Earlier reports indicated that some steroid substances could be thermogenic in rats, birds and in hibernators. In the rat, Freeman *et al.* (l970) demonstrated a thermogenic effect of progesterone, while Ohno and Kuroshima (1986) observed that metyrapone, an inhibitor of adrenal 11β-hydroxylase, causes an increase in oxygen consumption. Furthermore, it was found that deoxy-

corticosterone may contribute to non-shivering thermogenesis in hegdgehogs (Wünnenberg *et al.* 1974, Werner and Wünnenberg 1980). Hissa and Palokangas (1970) have shown that corticosterone had a stimulating effect on the oxygen consumption in the titmouse, but could not demonstrate the effect of this substance on body temperature of the pigeon.

Pyrogenic effects of etiocholanolone

When discussing the effect of steroids on heat production, one should mention a well-established pyrogenic effect of one of 17-oxo-steroids, 3α-hydroxy-5β-androstan-17-one (etiocholonanolone), known as etiocholonanolone fever. Etiocholanolone and several other 5β-reduced C_{19} steroids have been found to induce fever when administered to humans (Baullieu 1961, Kimball *et al.* 1966, Reimann 1968). The thermogenic effect of these steroids has been shown to be due to the release of interleukin-1 and other pro-inflammatory cytokines from the leukocytes that are mobilized in response to steroid administration (Steinetz *et al.* 1998). Glucocorticoids as endogenous antipyretics act in an opposite way (Roth *et al.* 2004). It is rather surprising that certain endogenous steroid metabolites possess such an effect, in contrast to many others, which do not. The detailed molecular mechanism of this phenomenon is unknown (Bondy and Bodel 1971). It does not seem, however, to be in any relation to UCPs; its mode of action may be central.

Corticoids and thermogenesis

More attention was devoted to the role of glucocorticoids, another group of hormones involved in the regulation of many metabolic processes in most body tissues. Generally, glucocorticoids stimulate catabolic processes and suppress utilization of glucose and other substrates. They play a key role in glycogen synthesis, gluconeogenesis, including stimulation of glucogenic amino acid release. In adipocytes, they stimulate lipolysis and reduce the number of glucose transporters. Recent studies demonstrated that glucocorticoids are also involved in the regulation of enzymes of oxidative phosphorylation in mitochondria (Scheller and Sekeris 2003). Glucocorticoids are also known stress hormones, which act in concert with catecholamines and many other hormones including those involved in rapid reaction to external temperature changes. In addition, glucocorticoids

are immunosuppressive and anti-inflammatory agents influencing biosynthesis and the release of various agents involved in immune response or during inflammation.

Most, but not all the effects of glucocorticoids consist in their regulation of the expression of various genes through interaction with glucocorticoid receptors and their binding to glucocorticoid responsive elements (GRE) in the DNA of regulated genes. Various enzymes as those involved in glycogen metabolism, gluconeogenesis, lipolysis, amino acid metabolism, but also membrane proteins such as the already mentioned glucose transporters, enzyme inhibitors (for instance lipocortins as specific inhibitors of phospholipase A_2 catalyzing the release of arachidonic acid from membrane phospholipids, serving as a substrate for prostanoids or leukotrienes), many peptide signaling molecules and, last but not least, various nuclear and transcription factors, are regulated by glucocorticoids in this way. As the latter protein factors are concerned, glucocorticoids bound to their receptors can repress several pro-inflammatory genes *via* protein-protein interaction with various transcription factors, without direct binding to GRE (Besedovsky and del Rey 1996, Pelaia *et al.* 2003).

With respect to manifold effects of glucocorticoids on one side, and the role of UCPs in modulating heat production on other, the question emerged, whether UCPs and their expression are also under regulatory control of steroid hormones. Most studies reported so far have dealt with the corticosterone effect (as a major glucocorticoid in rodents) on UCP1 expression in rat BAT under various conditions. Moriscot *et al.* (1993) studied the effect of corticosterone on UCP1 mRNA. The corticoid was given either to intact or to adrenalectomized rats, under normal temperature or after cold exposure or noradrenaline injection. While adrenalectomy alone did not affect UCP mRNA synthesis, corticosterone administration to adrenalectomized as well as to intact animals led to a remarkable decrease of UCP expression.

Pretreatment with corticosterone abolished the UCP mRNA response to cold as well as to noradrenaline. The data serve as clear evidence of the inhibitory effect of glucocorticoids on UCP gene transcription. Similar effects were observed with cultured brown adipose cells from hibernoma (HIB-1B) when using dexamethasone (Soumano *et al.* 2000). Surprisingly, the inhibitory effect on UCP1 expression was also shown by aldosterone in other hibernoma-derived T37i cells possessing functional endogenous mineralocorticoid receptors (Viengchareun *et*

al. 2001). An opposite effect on UCP1 expression had a synthetic antiglucocorticoid mifepristone (RU 486) on differentiated brown adipocytes in a steroid-free medium, confirming the previous conclusions that glucocorticoids affect UCP1 biosynthesis at least in part at the genomic level. The decrease of UCP2 expression in subcutaneous adipose tissue after treatment with prednisolone was also reported in humans (Udden *et al.* 2001). One fact should be stressed here: most of the effects of corticoids and thyroid hormones on UCP expression belong to relatively long-lasting genomic effects, which are characteristic for obligatory thermogenesis rather than a facultative one, of which the major regulators are catecholamines. For recent literature on this problem see Sell *et al.* (2004).

Sexual hormonal steroids and thermogenesis

The increase in body temperature of women in the perimenstrual period is ascribed to the mild pyrogenic effect of progesterone or its metabolites. Non-infection-related febrile morbidity in women with severe and critical ovarian hyperstimulation syndrome may be attributed to endogenous pyrogenic mechanisms after progesterone injection (Abramov *et al.* 1998). Rutanen *et al.* (1993) described two women who suffered from recurrent fever up to 40 °C in association with progesterone action and who have continuously elevated serum levels of immunoreactive tumor necrosis factor-alpha and interleukin-6 and suggested that cytokines cooperate with progesterone in exerting a pyrogenic response in the hypothalamic thermoregulatory center.

Experiments were performed to find whether sex steroids could affect UCP expression. Thus, in cultured rat brown adipocytes testosterone caused a dose-dependent inhibition of UCP1 mRNA induced by adrenergic stimulation with noradrenaline. The effect was reverted by androgen receptor antagonist flutamide, suggesting that at least in part testosterone acts *via* its receptor on a genomic level. Progesterone had an opposite effect but only at lower concentrations, while estradiol had no effect (Rodriguez *et al.* 2002). An inhibitory effect of testosterone on noradrenaline-induced UCP expression may be to some extent surprising, but it should be emphasized that the system studied need not reflect the situation *in vivo*, because events typical for the facultative thermogenesis (adrenergic stimulation) and for the obligatory one (mRNA expression *via* interaction with steroid receptors) are mixed here. *In vivo* adrenergic stimulation after corticoliberin (CRH) release, typical for

stress, activates the hypothalamo-pituitary-adrenal axis, and at the same time it suppresses many other functions as demonstrated by the inhibition of gonadoliberin (GnRH) or thyreoliberin (TRH) secretion and subsequent inhibition of gonadal and thyroidal axes. CRH also inhibits growth hormone secretion by the activation of somatostatin release (Tsigos and Chrousos 2002). Therefore the effect of testosterone and other sex steroids should be considered in the light of all the complex regulatory processes at stake.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) in a form of sulfate (DHEAS) is the most abundant circulating steroid in humans. Its levels decline dramatically with age, in parallel with degenerative changes related to aging. Longitudinal studies of association of lowered DHEA levels with various diseases, as well as intervention studies of DHEA replacement therapy, led to the conclusion that DHEA may possess various beneficial effects. It is believed now to be anticancer, antisclerotic, antidiabetic and an antiobese agent (Kalimi and Regelson 2000, Celec and Stárka 2003). DHEA and its sulfate are also potent neuroactive steroids through their modulatory effects on γ-aminobutyric (GABA) and N-methyl D-aspartate (NMDA) receptors (Morfin 2002b). Many but not all of these effects are ascribed to immunomodulatory or immunoprotective effects of DHEA, which in many instances acts as endogenous antiglucocorticoid counteracting the excessive actions of the latter hormones (Kalimi *et al.* 1994). Many studies have been undertaken in an attempt to elucidate the mechanism(s) responsible for these effects, but the data available so far indicate that DHEA acts at various sites and levels rather than by a unifying mechanism. Most of the experiments were carried out with rodents or cultured cells, in spite of the fact that DHEA/S levels in rodents are lower by several orders of magnitude than in humans (Kalimi and Regelson 2000).

From the above-mentioned DHEA effects we should mention its antiobesity action in rodents, consisting in both reduction of food intake and ineffective utilization/storage of ingested energy due to its possible action on UCP levels (Ryu *et al.* 2003). These authors studied the effect of DHEA on UCP1 expression and protein formation in BAT, and UCP2 and UCP3 in skeletal muscles, of obese and non-obese rats. The Otsuka Long Evans Fatty (OLETF) rats were used as an animal model of type 2 diabetes mellitus and obesity. Besides UCP mRNA and protein, mRNAs of two upstream regulators of facultative thermogenesis were also measured, namely β_3 adrenergic receptor (β_3AR) and peroxisome proliferator activating receptor γ or α (PPAR) coactivator 1 (PGC-1). Untreated obese rats displayed lower levels of UCP1 mRNA and protein than non-obese animals, and also a lower expression of both above mentioned activators. Feeding of obese rats with DHEA significantly increased UCP1 expression as well as that of both activators, but reduced UCP3 expression in skeletal muscles. The authors concluded that DHEA increases UCP1 expression in BAT by acting at multiple steps, especially through PPAR by increasing the expression of β_3AR and PGC-1. According to their data UCP1 (but not UCP2 and UCP3) plays an important role in the regulation of facultative thermogenesis. The results are consistent with the fact that DHEA is not a true hormone because it does not have its own receptors, or it competes with other hormones for their receptors (Kalimi and Regelson 2000). The significance of these results for humans, however, must be considered carefully, and further studies are needed concerning the plausible anti-obesity effect of DHEA.

Dehydroepiandrosterone metabolites as ergosteroids

Noteworthy among recent findings seems to be that of a strong effect of a group of DHEA metabolites bearing 7-oxo group called ergosteroids on metabolic pathways involved in thermogenesis (Lardy *et al.* 1995, 1998). The major representative of this group, 3β-hydroxy-5-androstene-7,17-dione (7-oxo-DHEA) has been known for years as a normal constituent of human blood, where it is present in the subnanomolar range (Marwah *et al.* 1999). It is an intermediate in oxidoreduction of other 7-oxygenated DHEA metabolites, namely its 7α- and 7β-hydroxyepimers (7-OH-DHEA). It may be of interest that the enzyme responsible for reduction of 7-oxo-DHEA to 7-OH-DHEA epimers, present mainly in the liver, is identical with peripheral Type 1 11β-hydroxysteroid dehydrogenase, catalyzing reduction of inactive cortisone to an active glucocorticoid cortisol (Robinzon *et al.* 2001).

For years 7-oxygenated DHEA derivatives have been considered only biologically inactive products of DHEA metabolism. In the past decade, however, evidence has accumulated that they may act as potent

local immunoprotective agents, being in fact responsible for many immunomodulatory and antiglucocorticoid effects hitherto ascribed to DHEA (Morfin 2002a).

Bobyleva *et al.* (1993) showed that DHEA modulates metabolic activities by increasing the activities of glycerol-3-phosphate dehydrogenase and mitochondrial malic enzyme, involved in transhydrogenation of cytosolic NADPH into mitochondrial FADH$_2$. Subsequently, the same group demonstrated that 7-oxo derivatives of DHEA, first of all 7-oxo-DHEA, are more active in this manner than the parent steroid (Lardy *et al.* 1995). In further experiments they have shown that 7-oxo-DHEA induced increased proton leak across the inner mitochondrial membrane (Bobyleva *et al.* 1997), similarly as thyroid hormones (Brand 1990). In rat liver the overall oxidation rate increased after steroid treatment while the amount of ATP formed was unchanged. Treatment of thyroidectomized rats with 7-oxo-DHEA could restore the effect of thyroid hormones (Bobyleva *et al.* 1997). In contrast to hormonal steroids mainly affecting the facultative thermogenesis as modulators of events starting by adrenergic stimulation, 7-oxo-DHEA (and to a lesser extent also DHEA) seems to induce predominantly the obligatory thermogenesis, but all the diverse mechanisms of this effect, especially its potential effect on UCP expression *in vivo*, should also be elucidated. We are preparing an experiment in an attempt to solve this question.

In some countries 7-oxo-DHEA is available without prescription as a trademark 7-keto DHEA. A study of its metabolism and pharmacokinetics in a group of healthy male volunteers given 7-oxo-DHEA in the form of acetate inidicated that it is well tolerated; the advantage over DHEA is that it is not metabolized to sex steroids (Davidson *et al.* 2000, Šulcová *et al.* 2005). With respect to its properties, 7-oxo-DHEA was even suggested for prevention of Raynaud´s attacks (abnormal digital vasoconstriction in response to cold) (Ihler and Chami-Stemman 2003).

It may thus be concluded that 7-oxo-DHEA is a potent thermomodulating agent, the final effect of which is comparable with thyroid hormones. Besides this, it is a precursor of other potentially beneficial steroids, thus rendering it one of perspective candidates of steroid replacement therapy.

Acknowledgements

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