IS THERE AN ESTROGENIC COMPONENT IN THE METABOLIC SYNDROME?

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ABSTRACT: *One of the major up-coming concerns leading to health related problems in the industrialized societies is the metabolic syndrome which is characterized by central obesity, hypertension, raised fasting glucose and triglyceride levels. The focus of this review is on a potential estrogenic linkage between the metabolic mechanisms involved into the development of this disease cluster and specific estrogen related regulatory pattern. The candidate molecules for this link are insulin and insulin-like growth-factor, C-reactive protein, peroxisome-proliferation-activating-receptor γ , and leptin which all seem to interact with each other and show a responsiveness to changing estrogen levels. From this perspective they might also represent target molecules for a phytochemical intervention with phytoestrogens.*

KEY WORDS: Estrogen, Metabolic syndrome, Obesity, Phytoestrogen

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INTRODUCTION

The metabolic syndrome or syndrome X is a multifactorial disease with a rising prevalence in western societies. The first description of a cluster of cardiovascular risk factors, especially hypertension, diabetes, dyslipidemia and obesity was given in the 1970s by Haller (Haller, 1977). Reaven described in 1988 this cluster of symptoms as "Syndrome X", suggesting insulin resistance as a cause of the syndrome since it occurred not only in obese patients with diabetes mellitus type II but also in non-obese individuals (Reaven, 1988). In 1998 the WHO, aware of growing evidence, developed a definition for the metabolic syndrome (Alberti and Zimmet, 1998) which was followed by a definition by the National Cholesterol Education Program (NCEP), suggesting an easier use in clinical practice (Anonymous 2001). The most recent definition incorporated ethnic-specific waist circumference cutoff points into the definition and the data

have been linked to other components of the metabolic syndrome in different populations (Federation, 2005). According to the worldwide definition of the International Diabetes Federation (IDF) a person with the metabolic syndrome must have central obesity and two of the following four factors: elevated triglyceride levels, reduced HDL cholesterol, increased blood pressure, elevated plasma glucose or type II diabetes. Additional metabolic criteria such as a proinflammatory and prothrombotic state for research are determined to allow further modifications of the definition and validation in different ethnical groups (Federation, 2005). In the USA the prevalence for metabolic syndrome is at the age group of 20 years and above at 24% which increases in subjects age 60 years and over up to 40% (Ford, et al., 2002). In Europe, Scheen et al and others (Bonora, et al., 2003, Scheen and Luyckx, 2003) estimated a prevalence of about 20% of all adults affected. The cost for the treatment of the symptoms in this disease will explode taking into account that in the USA already in the year 2000 the costs exceeded \$117 billion (Pearce, 2003). This makes the metabolic syndrome a major target for health research.

ESTROGEN

Many studies on estrogens and estrogenic compounds indicate that they have a major impact on the metabolism of lipids (Misso, et al., 2005b), but also on elements of the metabolic syndrome e.g. leptin function. Estrogens and estrogenic compounds act classically by binding to the estrogen receptors α and β (ER α and ER β), which change their conformation and dimerize. The dimer in turn binds with or without recruitment of cofactors to an estrogen responsive element (ERE) and thereby activates transcription (Nilsson, et al., 2001). In animal experiments it was shown that a lack of estrogen causes an increase of body fat resulting in obesity (Danilovich, et al., 2000, Heine, et al., 2000) and hypercholesterolemia (Hewitt, et al., 2003, Jones, et al., 2000). The increase in body fat weight combined to a changed distribution of fat depots to a more central android distribution can be observed in postmenopausal women as well (Gambacciani, et al., 1999, Gambacciani, et al., 2001, Gambacciani, et al., 1997). These effects might be mediated by the ER β (Liang, et al., 2002)

but research with estrogen receptor α knock out mice (α ERKO) points more towards an ameliorating effect of the ER β (Naaz, et al., 2002). On the other side the selective estrogen receptor modulator (SERM) Acolbifene exerts adiposity lowering and hypocholesterolemic effects via the ER α (Lemieux, et al., 2005). SERMs are compounds that exert estrogenic action in some tissues and antagonistic or no action in others (Nilsson, et al., 2001). These lipid lowering abilities are also shown for other SERMs (Reckless, et al., 1997, Sbarouni, et al., 2003). Mechanistically the weight gain might be explained by findings in ovariectomized mice where a down regulation of genes involved in both lipid synthesis and energy expenditure in adipose tissue was apparent (Kamei, et al., 2005). Aromatase knockout mice (ArKO) present a model of the metabolism in postmenopausal women with the metabolic syndrome. These mice lacking a functional Cyp19 gene which encodes aromatase (Fisher, et al., 1998) display underdeveloped uteri and an adipose phenotype with elevated levels of leptin, insulin and cholesterol due to a complete lack of estrogens (Jones, et al., 2000). All metabolic changes in ArKO mice are reversible by estrogen administration (Jones, et al., 2000, Misso, et al., 2003) and moreover feeding a cholesterol enriched diet prevents the characteristic obesity and decreases hyperplasia and hypertrophy of the adipose tissue (Misso, et al., 2005a). Human patients with aromatase deficiency show also adiposity, elevated cholesterol levels, impaired bone maturation and for the male patients hyperinsulinemia (Carani, et al., 1997, Maffei, et al., 2004, Morishima, et al., 1995). In a girl (Belgorosky, et al., 2003) but not in a boy (Deladoey, et al., 1999) with aromatase deficiency a decrease of the negative feedback for both serum LH and FSH was observed, that persists up to the sixth month of life for LH and for FSH during the rest of prepuberty. This was confirmed in ArKO mice (Fisher, et al., 1998). Female mice (ERKO, ARKO) (Rosenfeld, et al., 2001) as well as female humans (Belgorosky, et al., 2003, Morishima, et al., 1995) with aromatase deficiency develop ovarian cysts. All effects are reversible by estrogen administration (Belgorosky, et al., 2003, Bilezikian, et al., 1998, Carani, et al., 1997, Fisher, et al., 1998, Jones, et al., 2000, Maffei, et al., 2004, Morishima, et al., 1995) and at least partly reversible by phytoestrogens (Britt, et al., 2005). Phytoestrogens are plant derived substances that show estrogenic or antiestrogenic properties by binding to the ERs or by interference with estrogenic pathways (Miksicek, 1995, Shutt and Cox, 1972, Starcke, et al., 2002, van der Schouw, et al., 2000). Menopause and aging in women are associated with changes in the metabolism of abdominal and gluteal adipose tissue. It was shown that adipose tissue is able to produce increasing levels of estrogen with age at the time of menopause (Misso, et al., 2005a). The parallel increased levels of expression of adiponectin in the gluteal fat might lead to enhanced insulin sensitivity, which could be a physiological prevention of decreasing insulin sensitivity by estrogen depletion (Greenfield, et al., 2003, Misso, et al., 2005b). The well-known phytoestrogen genistein shows antiadipogenic effects by inhibiting the proliferation of adipocytes (Harmon and Harp, 2001) and promotes lipolysis (Szkudelski, et al., 2005). Here again an inhibitory impact of genistein on insulin-

related effects is discussed. But there seems to be an additional direct impact on glucose metabolism since ovariectomy in α ERKO mice improves insulin resistance and glucose tolerance (Naaz, et al., 2002). Already in the 1970s evidence was found that estrogen exposure to the perfused pancreas increases insulin release and that there is receptor binding for estrogen in the pancreatic islets (SutterDub, 1976, Tesone, et al., 1979). There might be a dual modulatory effect on the insulin release: enhancement directly by an interaction with the cytosolic estrogen receptor and inhibition indirectly after hydroxylation of estrogens to catecholestrogens, molecules with properties not shared by parental estrogens (Etchegoyen, et al., 1998). On the other hand differences in concentration or duration of exposure of islet cells to estradiol or progesterone are discussed to cause contradictory effects (Sorenson, et al., 1993).

INSULIN

Present knowledge about the metabolic syndrome is that hyperinsulinemia is a link between hypertension, obesity and impaired glucose tolerance (Modan, et al., 1985) and a regulation might be exercised by an interaction between leptin and the sympathetic nervous system (Haynes, et al., 1997, Landsberg, 1992, Landsberg, 1996). Additionally these symptoms are important risk factors for the development of chronic or acute heart failure (Kenchiah, et al., 2002, Taegtmeier, et al., 2002) which is causative connected with insulin resistance (Swan, et al., 1997). But there is also a strong indication that estradiol at physiological concentrations enhances glucose uptake in adipocytes at least in part at the step of insulin-induced tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1). At higher concentrations estradiol inhibits insulin-induced glucose metabolism which might be a possible explanation of insulin resistance in late pregnancy (Nagira, et al., 2006). The mechanism of this effect could be the inhibition of insulin signaling through phosphorylation of IRS-1 at Ser³⁰⁷. This serine³⁰⁷ is known to be phosphorylated by JNK, which is a crucial mediator of insulin resistance (Aguirre, et al., 2000). Hyperinsulinemia also might increase the risk of developing colorectal cancer (Hu, et al., 1999) since high insulin levels exhibited growth factor and tumor promoting properties in vitro (Koenuma, et al., 1989, Koohestani, et al., 1998, Tran, et al., 1996). For premenopausal women and postmenopausal women with hormone replacement therapy an estrogenic inhibition of insulin and IGF (insulin-like growth factor) at their membrane receptors or an interaction with the insulin- or IGF-system, including IGF binding proteins (IGFBP), IGF-Rs and IRS-1, is discussed. This could delay the growth promoting effects of insulin (Slattery, et al., 2003). At the same time estradiol causes an up regulation of IGF-1R and IRS-1. This enhanced presence of IRS-1 seems to involve an IGF-1R mediated increased proliferation (Molloy, et al., 2000). At least two signal cascades are involved in these effects: the phosphatidylinositol 3 (PI-3)-kinase-cascade and the MAP-kinase-cascade (Yamauchi, et al., 1996). This mechanism seems to be predominantly relevant for estrogen positive women with a BMI above 30, meaning that they are premenopausal or substituted with estrogen replacement

therapy, since this group is known to have a higher risk of developing colon carcinoma. Estrogen deficient women overall have a higher risk for colon carcinoma, but this was independent of the prevalence of obesity (Slattery, et al., 2003).

INSULIN LIKE GROWTH FACTOR (IGF)

Although IGF is not considered as a characteristic marker for the metabolic syndrome a significant correlation between lowered IGF levels and the prevalence of the metabolic syndrome exists (Sesti, et al., 2005). In premenopausal women the metabolic syndrome is associated with an increased risk of developing breast cancer (Kuhl, 2005). The impaired glucose tolerance which is a characterized by a number of changes in the glucose metabolism concerning the molecules insulin, IGF-1 and IGFBP, is discussed for a variety of mechanisms. Epidemiologic data suggest that elevated levels of IGF-1 and its corresponding IGFBP-3 in the serum of women are positively correlated with the risk of premenopausal breast cancer (Krajcik, et al., 2002). Both proteins do not contribute to postmenopausal breast cancer risk, in contrast IGFBP-2 seemed to have a protective effect (Krajcik, et al., 2002, Schairer, et al., 2004). One explanation for this phenomenon could be that mammary mRNA levels of IGF-1 and -2 are upregulated by estrogens which is correlated to a reduced rate of apoptosis in response to the survival factor IGF-1 and to enhanced proliferation in response to IGF-2. On the other hand levels of IGFBP-2, which are responsive to sex steroid hormones, are positively correlated to apoptosis and negatively to proliferation (Zhou, et al., 2001). The phosphorylation of Akt and MAPK as well as the induction of G1-S-phase progression which are essential for the mitogenic activity of IGF-1 is dependent on both IGF-1 and ER α and can be inhibited by the pure antiestrogen faslodex (Zhang, et al., 2005). Furthermore Kahlert et al demonstrated that activating the IGF-1R signaling cascade by phosphorylation requires the binding of estrogen to the ER α but not ER β (Kahlert, et al., 2000). On the other hand IGF-1 can activate ER α -mediated transcription of target genes independent of estrogenic ligands (Klotz, et al., 2002). With Rg1, a phytoestrogen from ginseng, it was shown that the mechanism of function for this substance involves the ER-dependent enhancement of the IGF-1R signaling pathway and thereby an increase of IGF-1R protein and mRNA expression (Chen, et al., 2006). Raloxifen, a selective estrogen receptor modulator, decreases IGF-1 levels in postmenopausal women with breast cancer (Torrise, et al., 2001). Even insulin at higher concentrations is able to bind IGF-1R and thereby activate the PI-3 kinase as well as a PI-3-independent signaling pathway leading to steroid hormone synthesis (Poretsky, et al., 2001). Variable IGFBP-1 levels during the rat estrus cycle (Molnar and Murphy, 1994) corroborate this theory of a estrogenic dependency. Estrogenic treatment causes a decrease of IGF-1 mRNA in rat liver (Krattenmacher, et al., 1994) while IGF-1 availability is affected by release of IGFBP-1 (McCarty, 1997). Furthermore the phytoestrogen genistein upregulates IGFBP-1 gene expression comparable to ethinylestradiol (Geis, et al., 2005) as well as a combination of different phytoestrogens increases IGF-1 levels (Woodside, et al., 2006).

C-REACTIVE PROTEIN

Subclinical inflammation can be confirmed in the majority of patients with a manifest metabolic syndrome (Tracy, 2003) although this marker is up to now not termed in the definitions. However, with an increase of CRP, which is synthesized in liver, a significantly increased risk for the metabolic syndrome is associated, although this is not significant after the adjustment of data for the body mass index (BMI) (Browning, et al., 2004). Still there is growing evidence that subclinical inflammation might be responsible for dysfunctions in lipid metabolism and moreover for the increasing risk of cardiovascular complications (Khovidhunkit, et al., 2000). There seems to be an interaction between CRP and estrogen since estrogen replacement therapy elevates serum CRP levels in ovariectomized rats as well as in postmenopausal women significantly (Lakoski SG, et al., 2005, Pradhan, et al., 2002, Yang, et al., 2005). Soy isoflavone application to postmenopausal women on the other hand ameliorated the levels of circulating CRP (Hall, et al., 2005), a feature shared by low doses of Tamoxifen, another SERM (Bonanni, et al., 2003). Further a non-steroidal estrogen receptor ligand that selectively inhibits the NF κ B transcriptional activity suppresses the induction of CRP indicating that the anti-inflammatory response is independent of ERE mediated transcription (Keith, et al., 2005). Both ERs are known to be able to modulate gene expression by interacting with for example NF κ B which prevents NF κ B from binding to the DNA and therefore inhibit transcription (Nilsson, et al., 2001). This pathway represses inflammatory immune response by a cross-coupling between the ER and NF κ B resulting in a reduced activity of promoters with ER binding sites (Stein and Yang, 1995). Overall it can be noted that CRP levels are higher in women than in men and that they are positively correlated with the BMI (Khera, et al., 2005). Additionally an improvement of elevated CRP levels can be achieved by insulin sensitizers in overweight patients with type II diabetes (Chu, et al., 2002) as well as in women with polycystic ovary syndrome (Morin-Papunen, et al., 2003). Both diseases comprise an insulin resistance syndrome which can be treated with insulin sensitizers such as thiazolidinediones. This decreasing effects of insulin sensitizers on CRP seem to be mediated again by NF κ B suppression (Ghanim, et al., 2001, Mohanty, et al., 2004). Furthermore appears the binding

of NF κ B to be positively correlated to the BMI, indicating that obesity is associated with a pro-inflammatory state, and to increasing insulin resistance which supports the possible role of inflammatory mediators like CRP in the development of diabetes (Ghanim, et al., 2004).

Peroxisome-proliferation-activating-receptor γ (PPAR γ)

The above mentioned thiazolidinediones are routinely used as antidiabetic compounds for patients with the metabolic syndrome which exert their insulin sensitizing activities via PPAR γ (Picard and Auwerx, 2002). Thiazolidinediones stimulate adipogenesis promoting a flux of free fatty acids from liver and muscle into the white adipose tissue. This decrease of triglycerides in liver and

muscle improves insulin sensitivity (Tsuchida, et al., 2005). It is also known that PPAR γ can inhibit the transactivation by the estrogen receptor through competition for ERE-binding (Keller, et al., 1995). In the uterus of ovariectomized mice treated with a combination of estradiol and Rosiglitazone, a PPAR- γ agonist, an increase in uterine mass and proliferation as well as a downregulation of ER γ was observed if compared to estradiol treatment alone (Gunin, et al., 2004). This indicates a cross-talk between the ER and PPAR- γ agonists although the mechanism remains to be elucidated. But this interaction works in both directions: the expression of ERs lowers basal and stimulated PPAR γ reporter-mediated activity in breast cancer cells (Bonofiglio, et al., 2005, Wang and Kilgore, 2002).

Interestingly for ER α this effect is enhanced after treatment with estradiol, while it is estradiol independent for ER β (Wang and Kilgore, 2002). The activated ER α is able to bind to the PPAR response element (PPRE) and thereby stimulate transcriptional activity (Bonofiglio, et al., 2005). Additionally the PPAR β ligand Troglitazone inhibits aromatase expression which catalyses estrogen biosynthesis (Rubin, et al., 2000). Also the phytoestrogen genistein at a micromolar range binds to and transactivates PPAR γ while at the same time downregulating ER transcriptional activity and thereby initiating adipogenesis in osteoprogenitor cells. An opposite effect can be seen at lower concentrations leading to the conclusion that the balance of both activated receptors determines the biological effects in these cells (Dang, et al., 2003). Furthermore for PPAR α (Andrade, et al., 2002, Faddy, et al., 2006) and PPAR δ (Stephen, et al., 2004) cross-talks with ER were found, possibly pointing to a general interaction pattern between these nuclear receptors (McKenna and O'Malley, 2002). Additionally PPAR γ and PPAR α are involved with the glucuronidation and thereby elimination of catecholestrogens by regulating the UDP-glucuronosyltransferase 1A9 (Barbier, et al., 2003). This mechanism of glucuronidation detoxifies the genotoxic steroid metabolites and prevents potential cell damages they can induce (Zhu and Conney, 1998). Furthermore hyperleptinemia downregulates PPAR γ expression in adipocytes and macrophages (Cabrero, et al., 2005, Zhou, et al., 1999).

LEPTIN

Another important and intensively discussed characteristic of the metabolic syndrome is leptin resistance. Leptin, a peptide with major influence on body weight, is synthesized and secreted by the cells of the white adipose tissue reflecting the total amount of this tissue by its circulating levels (Halaas, et al., 1995). It has potent effects on lipid metabolism and acutely increases glucose metabolism (Kamohara, et al., 1997). There is a strong indication that insulin resistance and leptin resistance are caused by interacting mechanisms. On the one hand leptin has a direct effect on the expression of insulin in pancreatic islet cells (Emilsson, et al., 1997) although in hyperinsulinemia serum leptin levels increase not acutely but within a period of three days (Kolaczynski, et al., 1996). Otherwise in an hypoleptinemic state such as in lipodystrophy diabetic symptoms and insulin resistance could be

reversed by application of leptin (Oral, et al., 2002, Shimomura, et al., 1999). Even further, Unger suggests that lipid-induced insulin resistance and the accompanying metabolic syndrome are secondary to leptin resistance which he sees as a mechanism to protect the organism of excessive lipid overload caused by eating habits (Unger, 2003) and sedentary lifestyle. Leptin is a robust indicator of BMI and insulin levels and the leptin level is inversely correlated with the activity of the hypothalamo-pituitary-adrenal axis (Korbonits, et al., 1997). This thesis is supported by the observation that in hypercortisolism leptin synthesis is increased (Veldman, et al., 2001). There are gender specific differences in leptin secretion, i.e. leptin levels are two- to threefold higher in women than in men (Considine, et al., 1996). Although there is this strong correlation between body fat and leptin level, additional results confirm the role of factors besides this monocausal explanation. In ovariectomized rats it was shown that substitution with estrogens could reverse elevated leptin levels to normal (Kristensen, et al., 1999). Since leptin receptor isoforms are found in gonadal tissue, including the long signaling form of the receptor, leptin could exert a direct endocrine action on the gonads (Kristensen, et al., 1999) which can also be shown by experiments on the reproductive abilities in partially starved mice (Cheung, et al., 1997). The essential role of leptin for the onset of puberty was also revealed in humans with a defect in the leptin receptor gene (Clement, et al., 1998). Leptin stimulates estrogen expression by increasing the aromatase expression (Catalano, et al., 2003) but also activates ER α and mimics the classic features of ER α transactivation through the MAPK pathway (Catalano, et al., 2004). Possible other mechanisms for the leptin-sex steroid hormone-interaction are the stimulation of the GnRH secretion by hypothalamic neurons, the secretion of gonadotropins by the pituitary gland, or by an indirect sensitization of the hypothalamus (reviewed by (Wauters, et al., 2000)). During the menstrual cycle leptin levels change in association with changes in sex hormones, namely estrogens (Mannucci, et al., 1998), progesterone (Cella, et al., 2000) and LH (Licinio, et al., 1998). Recently leptin and the leptin receptor were proven in human endometrium where their interaction seems to modulate reproductive functions by communication with the embryo (Gonzalez, et al., 2000). In adipocytes, the main producers of leptin, the phytoestrogen genistein diminishes the glucose- and insulin-induced secretion of leptin and at the same time raises the lipolysis in these cells. These effects might partly be due to an inhibitory activity of genistein on the cAMP/PKA pathway (Szkudelski, et al., 2005). Additionally Genistein has shown an antilipogenic effect in rat by reducing the weight of fat pads which require ER α (Naaz, et al., 2003).

ADDITIONAL CANDIDATE FACTORS CONNECTED

The liver X receptor α (LXR α) was found in adipose tissue, liver and skeletal muscle where it is involved in lipid and cholesterol metabolism (Peet, et al., 1998), regulates carbohydrate metabolism (Stulnig, et al., 2002) and thereby the nutritional status via for example PPAR γ (Chawla, et al., 2001) and leptin (Stulnig, et al., 2002). Interestingly the promoter activity of LXR α is

downregulated by estrogens and thereby causing a decreased level of its target genes in fat metabolism (Lundholm, et al., 2004). Another enzyme involved in fat metabolism is lipoprotein lipase which is localized both intracellular in adipocytes and extracellular on the surface of adjacent vascular endothelial cells. There it is responsible for the conversion of circulating triglycerides into free fatty acids. The activity of this enzyme depends on age, sex and the location of adipose tissue. This leads to the hypothesis that steroidal sex hormones particularly estrogens might affect lipoprotein lipase activity and thereby influence body fat distribution (Price, et al., 1998, Peinado-Onsurbe, 1993 #297).

Also different cofactors seem to play a role in the complex interaction networks of the metabolic syndrome such as PGC-2 which increases the transcriptional activity of PPAR γ as well as of the ER, and causes a dramatic increase of adipogenesis (Castillo, et al., 1999).

CONCLUDING REMARKS

Although the metabolic syndrome is considered to consist mainly of disorders in the glucose and lipid metabolism there are convincing hints on a connection to estrogen levels. One of the most important features in this syndrome is an accumulation of abdominal adipose tissue which is by now accepted not only as energy reservoir but also as an important organ with endocrine, paracrine and autocrine signaling. Adipocytes have a variety of receptors including ER, PPAR γ , IGF β , insulin and leptin receptors and they excrete an array of secretory products such as leptin and estrogen (reviewed by (Frühbeck, et al., 2001)). Therefore it seems reasonable to look for cross-talks between the involved metabolic pathways. For insulin, IGF, leptin and PPAR γ it is already

respond to estrogenic substances. Future research will probably reveal a complex signaling network leading away from the treatment of the single symptoms to a generalized disease management of the metabolic syndrome. Based on the fact that in traditional medicines ingredients of food like spices or herbs are used to cure a variety of diseases, modern science develops growing awareness towards these botanical products (Branca, 2003, Li, 2004 #304, Cassidy, et al., 2006, Kok, et al., 2005, Merritt, 2004). Research about phytoestrogens especially soy products is well established but also more knowledge towards improving blood lipids or glucose levels, such as associated with cinnamon (Khan, et al., 2003), is gained in the last years. The prospective for the development of medications consisting of the components of food seems promising.

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FIGURE. 1: Estrogenic effects on characteristic molecules in the mechanism of the metabolic syndrome

possible to verify links to estrogenic function as shown in this review (for an overview see figure 1) although the exact mode of action remains to be elucidated. But this is not only relevant for the adipose tissue since also general markers of the metabolic syndrome like the acute-phase proinflammatory protein CRP

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