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Aromatase up-regulation, insulin and raised intracellular oestrogens in men, induce adiposity, metabolic syndrome and prostate disease, via aberrant ER-α and GPER signalling

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ABSTRACT

For some years now, reduced testosterone levels have been related to obesity, insulin resistance, type 2 diabetes, heart disease, benign prostatic hypertrophy and even prostate cancer – often considered guilty more by association, than actual cause – with little attention paid to the important role of increased intracellular oestrogen, in the pathogenesis of these chronic diseases.

In the final stage of the steroidogenic cascade, testosterone is metabolised to oestradiol by P450 aromatase, in the cytoplasm of adipocytes, breast cells, endothelial cells and prostate cells, to increase intracellular oestradiol concentration at the expense of testosterone.

It follows therefore, that any compound that up-regulates aromatase, or any molecule that mimics oestrogen, will not only increase the activation of the mainly proliferative, classic ER-α, oestrogen receptors to induce adipogenesis and growth disorders in oestrogen-sensitive tissues, but also activate the recently identified transmembrane G protein-coupled oestrogen receptors (GPER), and deleteriously alter important intracellular signalling sequences, that promote mitogenic growth and endothelial damage.

This paper simplifies how stress, xeno-oestrogens, poor dietary choices and reactive toxins up-regulate aromatase to increase intracellular oestradiol production; how oestradiol in combination with leptin and insulin cause insulin resistance and leptin resistance through aberrant serine phosphorylation; how the increased oestradiol, insulin and leptin stimulate rapid, non-genomic G protein-coupled phosphorylation cascades, to increase fat deposition and create the vasoconstrictive, dyslipidemic features of metabolic syndrome; how aberrant GPER signalling induces benign prostatic hypertrophy; and how increased intracellular oestradiol stimulates mitogenic change and tumour-cell activators, to cause prostate cancer.

In essence, the up-regulation of aromatase produces increased intracellular oestradiol, increases ER-α activation and increases GPER activation, in combination with insulin, to cause aberrant downstream transduction signaling, and thus induce metabolic syndrome and mitogenic prostate growth.

To understand this fact, that raised intracellular oestradiol levels in men, induce and promote obesity, gynecomastia, metabolic syndrome, type two diabetes, benign prostatic hypertrophy and prostate cancer, rather than low testosterone, represents a shift in medical thinking, a new awareness, that will reduce the rising incidence of obesity, metabolic syndrome and prostate disease, and significantly improve the health of men worldwide.

1. Introduction

The incidence of obesity, metabolic syndrome, type 2 diabetes, heart disease, Alzheimer's disease, ovarian cancer, breast cancer and prostate disease are all increasing in frequency in the Western world.

Approximately 60% of adults are overweight or obese.

The incidence of obesity, with a BMI >30, or a waist circumference >102 cm for men or >88 cm for women, is more than 24% in the USA, Canada, Australia and the United Kingdom; whilst the incidence of combined overweight and obesity, with a BMI >25, exceeds 60% (World Health Organisation Global Infobase, 2004).

In other words, the excessive accumulation of subcutaneous and visceral fat reserves, seen in overweight and obesity, have become the new normal.

In turn, obesity-related medical conditions, including metabolic syndrome and type 2 diabetes, are on the increase, such that by 2025, more than 700 million people are expected to have metabolic syndrome, and one in 14 adults are projected to suffer from type 2 diabetes (International Diabetes Foundation, 2006). As such, heart disease, hypertension and stroke will continue to be the greatest cause of death and morbidity on a global scale.

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Approximately 80% of women and men will suffer from benign uterine and prostatic overgrowth conditions, whilst breast cancer and prostate cancer remain the most common malignant cancers in women and men, respectively.

This raging pandemic of suffering and financial burden, is now crippling some governments and smaller nations, where chronic disease is estimated to be responsible for 80% of the total disease burden and to represent 60% of the health expenditure (Health Priority Action Council (NHPAC), 2006).

Many of these chronic diseases have recently been associated with low testosterone levels, however little attention has been paid to the association of these chronic diseases with raised oestrogen levels; or to the processes by which the oestradiol, insulin, xeno-oestrogens, and cytokines, activate intracellular receptors to alter transcription, induce mitogenic change and stimulate anti-apoptotic properties, to cause obesity, metabolic syndrome and abnormal prostate growth.

This paper addresses the metabolic events and exogenous factors, which up-regulate P450 aromatase in adipocytes, endothelial cells, breast cells and prostate cells, to lower testosterone levels and increase intracellular oestradiol production; and how stress, xeno-oestrogen exposure and poor dietary choices increase oestradiol production to induce insulin resistance, leptin resistance and aberrant intracellular signaling cascades, to cause in effect, our current 21st-century epidemic.

2. Hormone homeostasis

In health, normal oestrogen levels are essential for fertility, normal endometrial and myometrial growth, subcutaneous fat distribution, female ductal breast growth, neuronal activation, osteoclast activity and neuromuscular excitability, whilst testosterone activates osteoblasts, muscle growth, cognitive function, neuronal activity and modulates sexual function and drive (Lange, 2010).

Insulin produced in pancreatic beta cells in response to reactive hyperglycaemia, increases glucose uptake by skeletal muscle and fat via recruitment of GLUT plasma membrane glucose transporters; converts glucose to glycogen; increases fatty acid synthesis; promotes lipogenesis; and normally modulates vasoconstriction and vasodilatation.

Leptin, an adipocytokine, is normally released by adipose cells to restrict appetite, or conversely, to stimulate appetite in the absence of fat reserves and adequate leptin levels.

When unopposed oestrogen levels increase, there is impaired fertility, increased endometrial and myometrial growth, increased fat deposition, increased breast growth and increased neuronal excitability. If testosterone levels deplete, muscle and bone growth are reduced, cognitive power and neuronal activity decrease, and sexual activity and energy are impaired.

With awareness that reduced levels of testosterone are catabolic processes that do not stimulate growth or endothelial dysfunction, it follows then that low levels of testosterone cannot cause obesity, insulin resistance, type 2 diabetes, heart disease, metabolic syndrome, benign prostatic hypertrophy (BPH) or prostate cancer; rather, it is the proliferative (Watson et al., 2008), vasoconstrictive (Kim et al., 2006), pathway-impairing, pathogenic actions of unopposed oestradiol in combination with insulin, that induce and promote these diseases – the focus of this research paper.

3. Oestrogen production and the significance of aromatisation

In the final stage of the steroidogenic cascade, testosterone is metabolised into oestradiol, (and androstenedione is metabolised into oestrone), by the enzymatic catalytic complex cytochrome P450 aromatase encoded by the cyp19 gene (aromatase-CYP19A1); the body's principal source of intracellular and systemic oestrogen.

Aromatase P450 is localised to the endoplasmic reticulum, in oestrogen-sensitive tissues such as adipocytes, breast cells, prostate cells and endothelial cells, conveniently adjacent to classical genomic oestrogen receptors, and to the more recently identified transmembrane G protein-coupled oestrogen receptors (GPER's) Prosnitz and Barton, 2009.

It follows therefore that any compound that upregulates aromatase will not only reduce testosterone, but also increase the intracellular biosynthesis of oestradiol, a known carcinogen (Watson et al., 2008; Dees et al., 1997). In turn, the increased intracellular oestradiol binds to ER-α in the classic genomic ligand–binding mechanism to stimulate increased transcription and promote excessive growth in oestrogen-sensitive tissues.

Similarly, any compound that increases the number or activity of oestrogen receptors, or any compound that alters the homeostatic balance of the transmembrane GPER activated cascade, will further increase growth, stimulate anti-apoptotic processes, and activate mitogenic change, metaplastic alteration and neoplastic activity, in oestrogen-sensitive tissues (Watson et al., 2007).

In the face of insulin resistance and leptin resistance, insulin and leptin are not recognised by their receptors (as if no insulin or leptin is present), even if they may be in excess, and so blood glucose and insulin levels increase, free fatty acid production is enhanced, glucose entry to cells is reduced, appetite is increased, and subcutaneous and intramuscular fat accumulation occurs.

4. The upregulation of aromatase

Insulin, cortisol, xeno-oestrogens, free fatty acids, inflammatory cytokines and oestradiol itself, all up-regulate the activity of aromatase, to effectively reduce testosterone levels and increase the intracellular concentration of oestradiol.

In essence,

- the injudicious dietary intake associated with the consumption of poor quality carbohydrates;
- the physical effects of illness, and/or the psychological stress associated with concern about love and acceptance, work pressure, financial stress and the perceived urgency of daily living;
- exposure to xeno-oestrogens, those insidious, foreign, oestrogen-like molecules, inhaled, applied or ingested in the form of pesticides, herbicides, benzenes, plastic by-products, and some pharmaceutical and cosmetic products, and also
- leptin, inflammatory adipocytokines, increased circulating free fatty acids, and oestradiol itself, the product of aromatisation.

ALL increase the activity of P450 aromatase, to TURBOCHARGE the production of endogenous intracellular oestradiol, accelerate fat deposition, and promote metabolic syndrome, type 2 diabetes, breast cancer and prostate disease.

5. Specific hormonal interactions that upregulate aromatase

The presence of rising intracellular bioactive oestradiol stimulates leptin production by fat cells (Tanaka et al., 2001), and together, they both upregulate 11β-hydroxysteroid dehydrogenase, (the enzyme that converts inactive cortisone into active cortisol), to significantly increase intracellular cortisol, and upregulate aromatase some 9-fold (Thornton et al., 2006).

In turn, and under stress, the increased cortisol and leptin output increases (see Fig. 1) compensatory eating and the desire

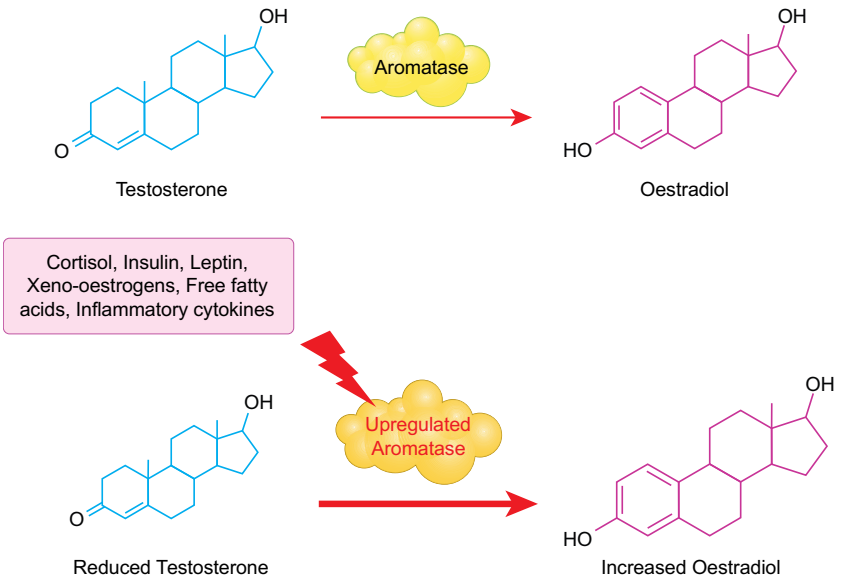

Fig. 1. p450 Aromatase up-regulation increases intracellular oestradiol. In the normal state, testosterone is aromatised into oestradiol by the catalytic action of aromatase, however the presence of cortisol, insulin, leptin, xeno-oestrogens, free fatty acids and inflammatory cytokines, upregulate the activity of aromatase, to effectively TURBOCHARGE the intracellular production of oestradiol, at the expense of testosterone.

to increasingly consume poor quality, high glycaemic "foods", only to increase insulin production and further up-regulate aromatase another 6-fold (Fig. 2).

Additionally, the increased oestradiol (Santner et al., 1997; Dieudonne et al., 2006; Kinoshita and Chen, 2003), and the increased leptin (Daghestani et al., 2007; Geisler et al., 2007) both upregulate P450 aromatase to further reduce testosterone levels and to increase extraglandular oestradiol production (Dieudonne et al., 2006; Catalano et al., 2003; Dundar et al., 2005), to increase subcutaneous fat deposition (Shin et al., 2007) and to potentiate the action of oestradiol on ER-α (Catalano et al., 2004; Sulkowska et al., 2006; Cirillo et al., 2008) and transmembrane G protein-coupled receptors (Vecchione et al., 2002).

Under normal homeostasis, there is a balance between cell regeneration and apoptosis; between vaso-constriction and vasodilatation; between lipolysis and lipogenesis; and between glucose entry into cells and cellular energy demand (Fig. 3).

However, over the last 20 years, the synergistic cyclic amplification of oestradiol, leptin, cortisol and insulin, and our exposure to endocrine disruptors have tipped our delicate hormone balance, to up-regulate aromatase, reduce testosterone, increase intracellular oestradiol production, promote oestradiol catechol formation, and to upset the normal homeostasis by overstimulating ER-α and GPER's, to induce cell changes in oestrogen sensitive tissues, from hypertrophy to neoplasia.

The physical effects of illness and inflammation, and the psychological stress associated with concern about being loved and accepted by family and peers, compounded by work pressure, financial stress and the perceived urgency of daily living, all contribute to effectively increase corticotropin releasing hormone (CRH) Foster et al., 2009. The resultant pituitary adrenocorticotrophic hormone (ACTH) and corticosterone output stimulate the increased consumption of sweet and palatable carbohydrates (Dallman et al., 2007), including foods that contain 30% sucrose (like many breakfast cereals, cakes, biscuits, and confectionary), that stimulate a normal reactive insulin response.

Unfortunately, the increased insulin output,

- upregulates P450 aromatase 6-fold (Samad, 2007),
- increases leptin output (Thomas et al., 2000; Falconnier et al., 2003; Manderson et al., 2003; Lindsay et al., 2004),
- increases ER-α number and activity (Kaaks, 2008),
- induces hypertriglyceridemia, sodium retention and hypertension (Biddinger and Kahn, 2006),
- increases subcutaneous fat deposition (Shin et al., 2007),

and activates aberrant signal transduction, cell production and anti-apoptotic processes by altering serine/threonine phosphorylation cascades of multiple tyrosine kinase receptors, acting through MEPK/ERK and PI3K/Akt/mTOR/NFkB pathways (Filardo et al., 2000; Filardo et al., 2007).

In effect, this process increases total fat mass, which enhances leptin production (Castracane et al., 1998) and amplifies oestradiol (Vona Davis et al., 2007) output.

The rising oestradiol,

- promotes insulin resistance (Ding et al., 2006; Livingstone and Collison, 2002),
- downregulates insulin receptor function (Hilf and Crofton, 1985),
- impairs insulin sensitivity (Gonzalez et al., 2002),
- increases pancreatic insulin gene expression and insulin biosynthesis (Nadal et al., 2000),
- inhibits insulin receptor gene expression in a dose and time dependent manner (Garcia-Arencibia et al., 2005),
- to create a reactive hyperinsulinemia, which inhibits leptin receptor expression (Ishida-Takahashi et al., 2006) by attenuating signal transducer and activating transcription factor (STAT3), that alters the downstream Jak-STAT signaling transduction cascade, thus promoting leptin resistance,
- and the resultant hyperleptinemia, (Banks et al., 2000; Kellerer et al., 2001; Fujita et al., 2003), rapidly activates aberrant phosphorylation of Akt in the PI3K/Akt/mTor (Uddin et al., 2010),
- and induces STAT3 phosphorylation (both of which transactivate cyclinD), to induce abnormal growth (Saxena et al., 2007a) and anti-apoptotic processes (Saxena et al., 2007b; Catalano et al., 2009).

Endocrine disruptors mimic the action of sex hormones (Nilsson, 2000). In particular, xeno-oestrogens, the foreign, man-made, oestrogen-like molecules, released into our food and environment in the form of pharmaceuticals, pesticides, herbicides, plastics, petroleum

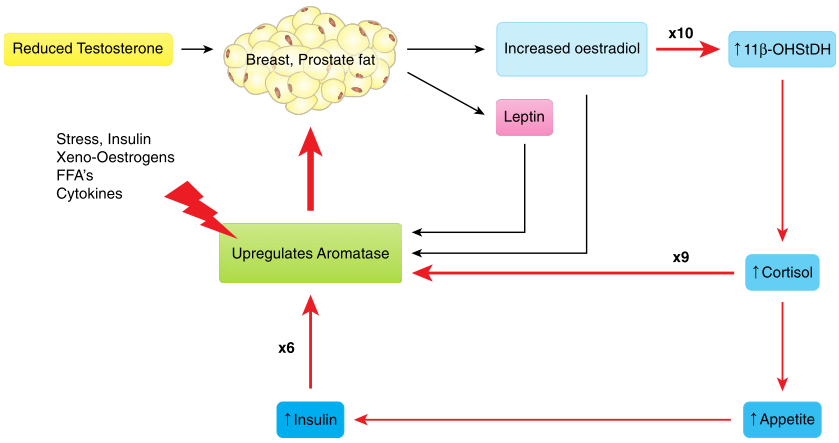

Fig. 2. Increased stress, appetite and foreign oestrogens, CYCLICALLY upregulate oestradiol production. Aromatase up-regulation increases intracellular oestradiol concentration, which in turn up-regulates 11-β hydroxysteroid dehydrogenase 10-fold, to create increased cortisol, which further up-regulates aromatase 9-fold and also increases appetite for poor quality carbohydrates and reactive insulin production, which in turn up-regulates aromatase another 6-fold. . .to cyclically up-regulate aromatase, further reduce testosterone and produce even more oestradiol.

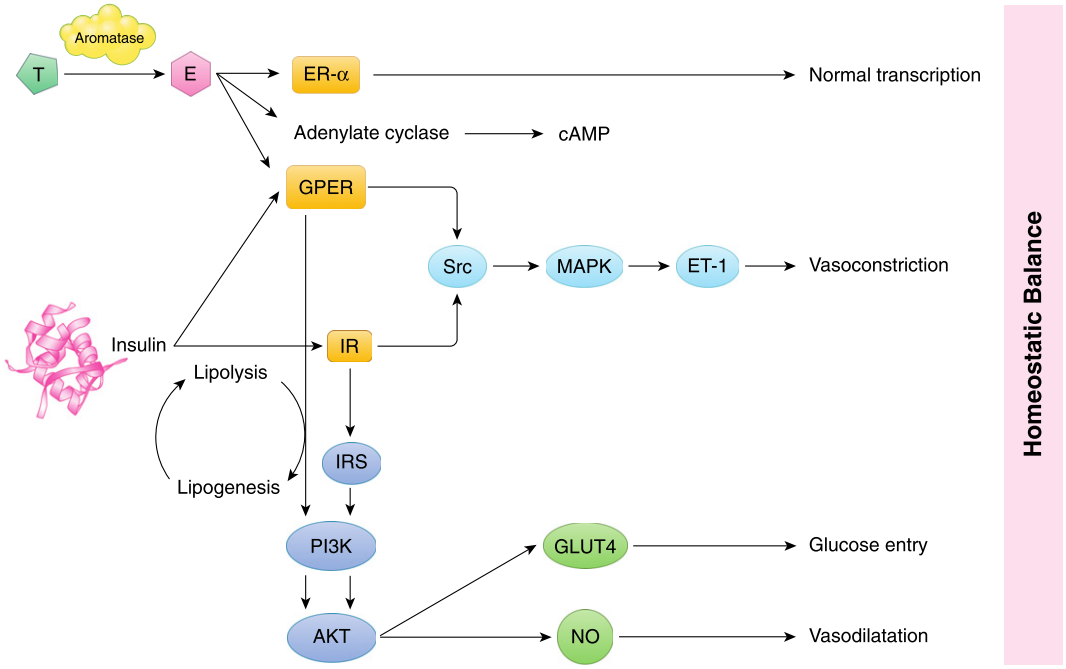

Fig. 3. PI3K/AKT/NO/GLUT4 and MAPK/ET-1 pathways in healthy balance. In homeostatic balance, normal intracellular oestradiol levels activate ER-α and GPER to produce normal transcription, and together with insulin they act via GPER to balance the vasoconstrictive effects of MAPK/ET-1 production, with Akt/NO output-mediated vasodilation, together with GLUT4 activation, to effect optimal glucose cell entry and haemodynamic vascular control. T, Testosterone; E, Oestradiol; ER-α, oestrogen receptor alpha; GPER, G protein-coupled estrogen receptor; Src SRC, Homology 2; MAPK, mitogen activated protein kinase; ET-1, endothelin-1; IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphotidylinositol 3-kinase; Akt or PKB, protein kinase B; NO, nitric oxide.

chemicals and agricultural growth enhancers, often without regard for environmental damage or the cost to human health.

Politely called environmental chemicals, they exhibit potent, lipophilic, fat-soluble, long half-life properties, with powerful ER-α, PXR (pregnane X receptor) (Kojima et al., 2010) and/or GPER agonist activity (Watson et al., 2007).

Furthermore, they have been shown to up-regulate P450 aromatase expression, and act as an initiator of significantly raised intracellular oestradiol production in adipose (Newbold et al., 2008, uterine (Laville et al., 2006), prostate (Prins, 2008) and breast tissue (Kinoshita and Chen, 2003).

The common commercial chemicals, bisphenol A, butyl benzyl phthalates, dioxin 2,3,7,8-TCDD, cadmium, arsenicals, nonylphenol, octophenol; and the PCB industrial chemicals, endosulfan, lindane, parathion, dieldrin, and DDT insecticides; hexachlorobenzene, maneb, and tributyltin fungicides; and 2,4,-D, 2,4,5,-T, and atrazine herbicides, to name a few, are all endocrine disruptors (Bouvard et al., 2009).

Even UV filters are a class of endocrine active chemicals, in particular 4-methylbenzilidine camphor (4-MBC) and octyl-methoxycinnamate (OMC), shown to display dose-dependent oestrogenic action in MCF-7 human breast cancer cells, and to affect oestra-

diol-regulated genes in the prostate and uterus (Schlumpf et al., 2004).

As adipogenesis increases under the action of up-regulated P450 aromatase and raised intracellular oestradiol, the adipocyte releases increasing quantities of leptin and free fatty acids (FFA's) that activate nuclear transcription factor nuclear factor kappa beta (NFkB) in adjacent macrophages, which further upregulate aromatase via COX-2/PGE2, IL-1β and TNF-α (Suganami and Ogawa, 2010).

In summary, continuing exposure to stress, compensatory eating, xeno-oestrogens, the pill, pesticides, oestrogenic chemicals, fast foods, soft drinks and poor quality carbohydrate diets, cyclically amplify aromatase to TURBOCHARGE the production of even more oestradiol...until overweight becomes obesity, stress becomes depression, glucose intolerance becomes type two diabetes, benign prostate and breast changes turn into prostate cancer and breast cancer, and acceptable forgetfulness progresses toward Alzheimer's disease.

The up-regulation of aromatase produces increased intracellular oestradiol, increases ER-α activation, and increases GPER activation in combination with insulin, to cause aberrant downstream transduction signaling to induce the clinical changes of metabolic syndrome and mitogenic prostate growth.

Over recent years, low testosterone levels have been significantly associated with many chronic diseases, and it has dominated medical opinion, with little attention being paid to the role of increased intracellular oestrogens in the pathogenesis of our most common chronic diseases.

Although testosterone is inversely proportional to:-

- obesity (Corona et al., 2009; Phillips et al., 2003),
- insulin resistance (Phillips et al., 2003; Haffner et al., 1994a,b; Osuna et al., 2006),
- type 2 diabetes (Dhindsa et al., 2004),
- heart disease (Hak et al., 2002),
- dyslipidemia (Phillips et al., 2003; Laaksonen et al., 2003),
- prostate cancer (Schatzl et al., 2001),

it is important however, to realise that testosterone is also inversely proportional to oestradiol, and as such, the author maintains that all of these diseases are actively caused by, or pathogenically linked to, raised unopposed intracellular oestrogen levels, and not necessarily low testosterone levels (Williams, 2010).

Let us consider the evidence of raised oestradiol and reduced testosterone levels in chronic disease states.

6. Obesity

Obesity, raised BMI, high fat percentage, and increased hip circumference are all strongly correlated to increased oestradiol levels (Key et al., 2003), and the rising intracellular oestradiol activates ER-α to stimulate adipogenesis (Iguchi et al., 2008).

The same hormone, produced by ovarian cells at puberty to stimulate breast, nipple and ductal growth in pubertal girls, is also produced in excess by fat cells in middle-aged men, to induce gynecomastia and nipple enlargement.

Oestrogen increases the deposition of subcutaneous fat (especially on the hips, upper thighs and lower abdomen); ectopic fat in the liver and muscle; and visceral fat in and about abdominal organs (Daghestani et al., 2007; Dyck et al., 2006). As the enlarging fat cells produce more oestradiol (Carr and Bradshaw, 2005), they increase their leptin output (Tanaka et al., 2001), to cyclically up-regulate 11β-hydroxysteroid dehydrogenase (Dieudonne et al., 2006) and aromatase (Catalano et al., 2003), increase intracellular cortisol and oestradiol production (Thornton et al., 2006), and promote insulin resistance (Livingstone and Collison, 2002) and leptin resistance (Ishida-Takahashi et al., 2006).

Whilst obesity and subcutaneous fat deposition are associated with an increased ER-α to ER-β ratio (Shin et al., 2007), higher fat percentages and increased hip circumference are not only related to raised oestradiol, they are strongly correlated with increased leptin (Ho et al., 1999), and hyperinsulinemia (Borugian et al., 2003).

7. Insulin resistance and type 2 diabetes

Raised endogenous oestrogen levels and xeno-oestrogen exposure, in concert with increasing adipocyte leptin and cytokine release, inhibit insulin receptor function to initiate insulin resistance.

Raised levels of oestrogens (seen in obesity and contraceptive/HRT use) (Ding et al., 2006), promote insulin resistance (Livingstone and Collison, 2002), down-regulate insulin receptor function (Hilf and Crofton, 1985), impair insulin sensitivity (Gonzalez et al., 2002), increase insulin biosynthesis (Nadal et al., 2000), and inhibit insulin receptor expression (Garcia-Arencibia et al., 2005), to directly cause insulin resistance and promote type 2 diabetes.

Triphasic ethinyl-oestradiol oral contraceptive use for six months reduces insulin sensitivity, increases insulin levels and induces glucose intolerance in 10% of users (Petersen, 2002).

The increasing leptin down-regulates insulin action by phosphorylating the serine 318 residue of insulin receptor substrate (Hennige et al., 2006), to impair the PI3K/Akt pathway (Kim et al., 2006), which normally activates GLUT4 to facilitate cellular glucose uptake and vasodilatory nitric oxide synthase function, to induce insulin resistance and reactive vasoconstriction.

The raised oestradiol and the resultant hyperinsulinemia, inhibit leptin receptor signaling via attenuation of STAT3 phosphorylation on serine 523 (Ishida-Takahashi et al., 2006), to promote leptin resistance (Fujita et al., 2003), only to encourage the inappropriate consumption of further high carbohydrate, low-nutrition 'food'. In turn, the increased leptin (Cirillo et al., 2008) and insulin (Samad, 2007) cyclically up-regulate aromatase in fat, breast and prostate cells, to produce more intracellular oestradiol, more growth, increasing insulin resistance and eventually type 2 diabetes.

Obesity, increased fat, elevated BMI and larger hip circumferences are all closely linked to raised oestradiol levels and to the incidence of type 2 diabetes, such that women with low oestradiol levels have 80% less risk of developing type 2 diabetes, and men have 52% less risk (Ding et al., 2006). Importantly, short-term aromatase inhibition has been shown to halve oestradiol levels, lower insulin and reduce leptin levels, and to improve glucose homeostasis (Lapauw et al., 2009).

Taken together, stress, poor diet and xeno-oestrogen exposure, contribute to excess intracellular endogenous oestradiol production, that stimulates adipogenesis, and increased leptin, insulin and oestradiol production, which interferes with insulin signaling to promote insulin resistance and induce type two diabetes (Williams, 2010).

8. Metabolic syndrome and heart disease

The criteria for metabolic syndrome, including,

- central obesity, with a waist circumference >102 cm for men and >88 cm for women,
- hypertension, >130 mmHg systolic and >85 mmHg diastolic,
- raised triglycerides >1.7 mmol/l,
- lowered HDL-cholesterol, <1.03 mmol/l, and
- raised glucose levels, >6.1 mmol/l (National Cholesterol Education Program, 2002),

represent a cluster of clinical findings primarily associated with insulin resistance and endothelial dysfunction.

Although low testosterone has been associated with metabolic syndrome, it is important to realise that testosterone is metabolised by aromatase in fat cells, breast cells, prostate cells and endothelial cells, to increase intracellular oestradiol levels; and that these raised oestradiol levels are directly induce fat deposition, insulin resistance and endothelial dysfunction.

The rising oestradiol concentration increases adipogenesis and the formation of large dysfunctional adipocytes that produce increasing amounts of leptin, angiotensin and pro-inflammatory cytokines, which stimulate ectopic fat deposition in skeletal muscle and liver sites (Pausova, 2006) and activate hepatic C-reactive protein to promote cardiovascular disease (Bastard et al., 2006).

Although oestrogen has long been considered atheroprotective, research has now identified increased aromatase expression and increased local oestradiol production in fibroatheromatous plaques, adjacent smooth muscle and thickened human aortic intima (Murakami et al., 2001), which serve to facilitate plaque formation, intimal disruption and to increase thrombolic risk.

The oestrogen and leptin combine to induce insulin resistance via abnormal phosphorylation of serine 318 on insulin receptor substrate (IRS), to inhibit normal insulin receptor signaling, and to increase the output of ineffective insulin. To complicate matters further, the reactive hyperinsulinemia induces aberrant JAK-2 (Janus-Kinase-2) serine 523 phosphorylation, to induce leptin resistance and to increase the output of ineffective leptin, and as leptin resistance increases, so does the risk of heart failure, coronary heart disease, cerebrovascular disease and overall mortality (Lieb et al., 2009).

As noted previously, oestradiol promotes fat deposition, insulin biosynthesis leptin production and inflammatory adipocytokine release, primarily by aromatase up-regulation and subsequent ER-α stimulation, independent of its actions upon the seven transmembrane G protein-coupled oestrogen receptor, an intracellular tyrosine kinase receptor with multiple cognate ligands, most notably, oestradiol, insulin, leptin and a raft of xeno-oestrogens.

GPER activation is normally under homeostatic control in healthy tissues, to create a balance between vasoconstriction (mediated by the Ras/MAPK/ET-1 pathway), and vasodilation (mediated by the PI3K/Akt/nitric oxide pathway) by modulating a complex cascade of serine/threonine residue phosphorylations (Kim et al., 2006; Prosnitz and Barton, 2009).

Unfortunately, oestradiol (Watson et al., 2008), leptin (Vecchione et al., 2002), insulin (Kim et al., 2006) and foreign oestrogens (Watson et al., 2007), induce abnormal activation and aberrant signaling to disrupt the homeostasis, in favour of vasoconstriction, excessive cell proliferation, inhibited apoptosis, free fatty acid and diacyl glycerol production, and a cascade of mitogenic and inflammatory cytokine release, which in effect, directly cause endothelial changes, dyslipidemia, angiotensin 2 production, hypertension, glucose intolerance, oxidative stress, shear factor changes, and erectile dysfunction.

9. Erectile dysfunction

Erectile dysfunction is essentially an endothelial disorder with impairment to vasodilation; a condition closely associated with insulin resistance, type 2 diabetes (Eaton et al., 2007), metabolic syndrome – obesity, hypertension, dyslipidemia (Eaton et al., 2007; Al-Hunayan et al., 2007), and future cardiovascular events.

In fact, erectile dysfunction is three times more common in men with metabolic syndrome (Demir et al., 2006; Esposito et al., 2005), being directly related to waist circumference and higher waist/hip ratios (Bal et al., 2007; Heidler et al., 2007), and associated with oestrogenic fat deposition (Key et al., 2003), aggravated by reduced HDL-cholesterol and elevated triglyceride dyslipidemia (Eaton et al., 2007).

Although low testosterone is associated with erectile dysfunction, the primary cause is inadequate endothelial nitric oxide concentration, due to reduced production or increased degradation, directly linked to aberrant downstream GPER activation by oestradiol and insulin, aggravated by inflammatory adipocytokines and circulating free fatty acids.

In health, neuronal and endothelial nitric oxide synthase catalyses the conversion of arginine into citrulline and nitric oxide, to initiate and maintain erections. The nitric oxide diffuses into smooth muscle cells where it activates an intracellular calcium flux (via cyclic guanosine monophosphate cGMP) to induce smooth muscle relaxation, promote engorgement of corporal vessels and produce effective erections.

Phosphosdiesterase-5 (PDE-5) degrades cGMP to produce detumescence; hence the use of pharmacological PDE-5 inhibitors to preserve nitric oxide levels (and erections), by delaying degradation.

As previously mentioned, the normal GPER stimulation activates two complex serine/threonine phosphorylation cascades, basically proceeding via MAPK to produce the vasoconstrictor ET-1, and via PI3K/Akt/nitric oxide to produce vasodilatation (Fig. 3).

In conditions associated with raised oestradiol, insulin and leptin levels, (aggravated by free fatty acids and adipocytokines), aberrant intracellular transduction signaling in the PI3K/Akt/nitric oxide pathway and increased nitric oxide degradation occurs, to inhibit effective nitric oxide concentration and vasodilation. Unfortunately, the mitogenic, vasoconstricting MAPK/ET-1 pathway remains highly active (Kim et al., 2006), to create predominant vasoconstriction and thus increase peripheral resistance in systemic vascular beds, and to stimulate abnormal endothelial and perivascular adipocyte proliferation – in essence, hypertension, atherosclerotic change, obesity, insulin resistance, dyslipidemia and erectile dysfunction, the hallmarks of metabolic syndrome and cardiovascular disease (Fig. 4).

10. Prostatic hypertrophy and prostate cancer

Although benign prostatic hypertrophy (BPH) and prostate cancer have long been attributed to an excess of testosterone, there is no clinical evidence of any increased incidence, or any exacerbation of BPH or prostate cancer, associated with testosterone supplementation (Morley, 2000; Rhoden and Morgentaler, 2004). The days of blaming testosterone alone for prostatic disease have passed.

Prostate cells, both normal and malignant, exhibit ER-α, ER-β and GPER's, and contain the essential enzymes to convert dehydroepiandrosterone to oestradiol, in particular 17β-hydroxysteroid dehydrogenase and aromatase.

Oestrogens initiate and promote benign prostatic hypertrophy (BPH) Hammarsten et al., 2009. The principal role in aberrant cell proliferation and metaplastic change, rests with increased intracellular prostatic oestradiol, due to increased expression and up-regulation of prostatic aromatase (Risbridger and Bianco, 2003), and its subsequent divergent activation of ER-α more than ER-β (Carruba, 2006), together with GPER activation, to stimulate nuclear transcription and increased cell proliferation.

ER-α activation stimulates BPH, inflammation and prostate cancer, whilst ER-β activation tends to be inhibitory (Ellem and Risbridger, 2007). Reduced ER-β expression, and hence reduced growth inhibition, has been observed in prostate cancer (Bardin et al., 2004). Similarly, ER-β expression progressively declines in localized prostatic cancer, as Gleason scores increase from

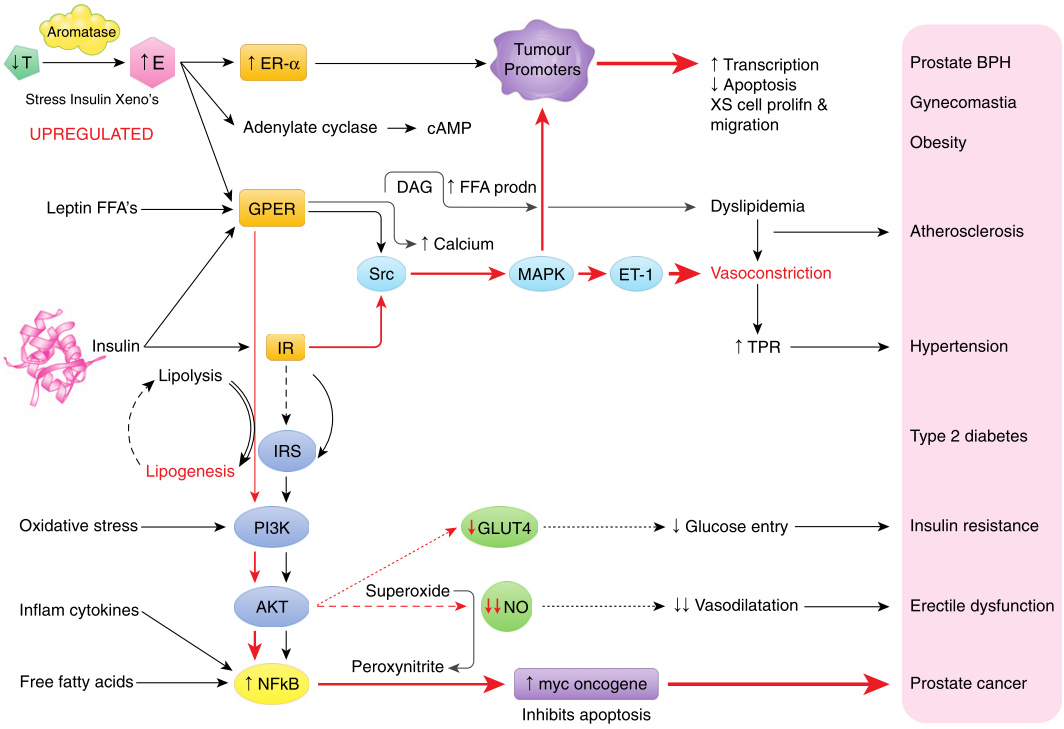

Fig. 4. Oestrogen-induced pathogenesis of metabolic syndrome/prostate disease. When intracellular oestradiol levels are increased by aromatase up-regulation, ER-α, adenylate cyclase and GPER/MAPK are overstimulated, but the PI3K/Akt/NO/GLUT4 pathway is inhibited, to tip the haemodynamic balance in favour of vasoconstriction, and in combination with insulin, to activate mitogenic tumour promoters and oncogenes, which stimulate aberrant growth and reduced apoptosis in adipocytes, endothelial cells, prostate tissue. DAG, DiAcylGlycerol; FFA, free fatty acids; TPR, total peripheral resistance; NFkB, nuclear factor kappa beta.

prostatic intraepithelial neoplasia to advanced prostate cancer (Prins and Korach, 2008.

Oestradiol, insulin, leptin and xeno-oestrogens not only up-regulate aromatase to promote cell proliferation via ER-α activation, they also activate the same aberrant GPER signaling pathways that cause metabolic syndrome, to initiate and promote BPH and prostate cancer.

Metabolic syndrome is closely associated with the incidence of BPH, such that the degree of BPH is also proportional to obesity, hypertension, raised insulin, raised triglycerides and lowered HDL-cholesterol (Ozden et al., 2007), and that serum insulin levels are proportional to prostatic volume (Hammarsten et al., 1998). Similarly metabolic syndrome doubles the risk of prostate cancer (Laukkanen et al., 2004); a BMI over 27 triples the risk (Laukkanen et al., 2004); and prostate cancer staging and grades are proportional to BMI, waist circumference, insulin (Hammarsten and Högstedt, 2005) and triglyceride levels, and inversely proportional to HDL cholesterol and testosterone levels (Hammarsten and Högstedt, 2004).

Low testosterone levels rather than high testosterone levels are associated with prostate cancer (Schatzl et al., 2001). In fact, lower testosterone levels are correlated with positive prostate biopsies and higher Gleason scores (Gustafsson et al., 1996), whilst men with higher testosterone levels have a reduced risk of prostate cancer (Stattin et al., 2004).

On the other hand, obesity and leptin increase the incidence and aggressiveness of prostate cancer (Mistry et al., 2007), and men with a BMI above 30 have a 78% increased risk of high grade prostate cancer, with a Gleason score above 8 (Gong et al., 2006).

The synergistic actions of oestradiol together with insulin and leptin, seen in men with higher waist-hip ratios, higher percentage fat and metabolic syndrome, have an 8.55 fold increased risk of prostate cancer (Hsing et al., 2001); and raised free oestradiol levels increase prostate cancer risk (Gann et al., 1996), as do lipophilic, fat-soluble oestrogenic pesticides and environmental endocrine disruptors (Imigaray et al., 2007; Prins, 2008).

In essence then, it's not the testosterone that causes prostate cancer, but the aromatase up-regulation that lowers testosterone levels and increases intracellular prostatic oestradiol, which in turn stimulates prostatic ER-α and rapid mitogenic non-genomic GPER pathways, to directly induce prostatic basal cell hyperplasia, and to promote cellular proliferation and metaplastic change.

11. Summary

In health, GPER activation stimulates cascading serine/threonine phosphorylations to facilitate rapid (seconds to minutes) non-genomic intracellular transduction signals designed to achieve homeostasis between cell growth and apoptosis, circulating glucose and insulin, lipogenesis and lipolysis, and responsive vasoconstriction and vasodilatation of vascular beds.

However aromatase upregulation, and raised intracellular oestradiol and insulin, (together with leptin, xeno-oestrogens, increased circulating free fatty acids and inflammatory cytokines), cause abnormal phosphorylation sequences to occur on different serine/threonine residues, which induces conformational change, aberrant signaling, altered feedback and crosstalk, down-regulation of vascular control and insulin function, and upregulation of mitogenic kinases and tumour growth factors, to promote abnormal cellular proliferation, increase cell migration and inhibit apoptosis.

So a combination of stress, poor diet, pesticide exposure, free fatty acids and inflammatory cytokines can upregulate aromatase in adipocytes, breast cells, prostate cells and endothelial cells, to lower circulating testosterone levels and increase intracellular oestradiol, which activates cytoplasmic ER-α to stimulate nuclear translocation, subsequent transcription and increased cell growth; and also activates the nearby endoplasmic reticulum transmembrane tyrosine kinase receptors, now called GPER, to unleash an abnormal phosphorylation cascade, that stimulates aberrant growth in the affected tissues, compromises vasodilatation,

increases vasoconstriction, induces insulin resistance, triggers dyslipidemia, and induces mitogenic growth factors and metaplastic change in breast and prostate cells.

In other words, the same pathways that cause obesity, metabolic syndrome, erectile dysfunction and type 2 diabetes, also initiate prostatic hypertrophy and prostate cancer.

Oestrogenic fat deposition leads to overweight and obesity; endothelial growth, endothelial dysfunction and dyslipidemia lead to atherosclerosis; and together with unopposed ET-1 vasoconstrictive drive, they cause hypertension, heart disease and erectile dysfunction – the hallmarks of metabolic syndrome. Insulin resistance and leptin resistance progress to further up-regulate oestrogenic ER-α and GPER growth stimuli, which initially stimulate benign breast growth (gynecomastia) and benign prostatic hypertrophy; but in time, they induce aberrant growth and metaplastic change which can progress to breast cancer and prostate cancer.

Over recent decades, the synergistic cyclic amplification of oestradiol, leptin, cortisol and insulin, and our exposure to endocrine disruptors have tipped our delicate hormone balance, to up-regulate aromatase, reduce testosterone, increase intracellular oestradiol production, promote oestradiol catechol formation, and to upset the normal homeostasis by overstimulating ER-α and GPER's, which induces cell changes in oestrogen-sensitive tissues, from hypertrophy to neoplasia.

The awareness that raised intracellular oestradiol levels in men, induce and promote obesity, gynecomastia, metabolic syndrome, erectile dysfunction, type 2 diabetes, benign prostatic hypertrophy and prostate cancer, rather than low testosterone levels, represents a paradigm shift in medical thinking, that can reduce unnecessary suffering, decrease wasted health expenditure and help prevent obesity, metabolic syndrome and prostate disease in men worldwide.

Disclaimers

Dr. Graeme P. Williams is the sole author of this paper. No medical writers or editors have contributed to this work. Dr. Graeme Williams confirms that he had total access to all aspects of this research paper, and that he holds total responsibility for the decision to submit this paper for publication.

Conflict of interest statement

The author, Dr. Graeme P. Williams, has no conflict of interest associated with the contents or publication of this paper. All research and written production was performed by, and self-funded by, Dr. Graeme Williams. The diagrams are originals with enhanced artwork performed by Elsevier Webshop.

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