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Editorial Open Access

Insulin Resistance in Women with Polycystic Ovary Syndrome: Optimising treatment by Implementing an *in vitro* Insulin Resistance Organ Culture Model

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Editorial

Polycystic ovary syndrome (PCOS) affects about 5-10% of fertile women and is characterised by insulin resistance (IR), dyslipidaemia, hyperandrogenism, and oligomenorrhoe. The metabolic disruption in PCOS women requires treatment to prevent the progression of IR to diabetes and cardiovascular disease. Metformin is currently first line treatment for metabolic/glycemic abnormalities, but lacks beneficial effect on IR PCOS patients with side-effects and cost outweighing benefits. Rosiglitazone has shown to reduce IR,but it was recently withdrawn from the market due to severe side-effects. Basic research into developing optimised drug treatments for IR in PCOS is critical to reducing the development of PCOS associated diabetes and cardiovascular disease. Testing and optimising drugs to reduce IR in PCOS patient samples is difficult due to ethical restrictions. In vitro organ culture models are valuable and reliable. Coronary arteries incubated with high doses of insulin and glucose will be screened for reliable intracellular IR associated biomarkers by western blot and real time PCR analysis. Vascular function by wire-myograph analysis will validate endothelial dysfunction and assess myocardial vascular injury associated responses. The associated response to clinically relevant anti-diabetic treatment options and adjunct therapy will be investigated. Developing a PCOS IR simulated organ culture model will enable us to understand the complicated intracellular signalling mechanisms leading to IR and may lead to development of potential new drug therapy options improving the PCOS IR treatment outcome.

Keywords: Polycystic ovary syndrome; Insulin resistance; Cardiovascular diseases; Insulin resistance organ culture model; Insulin resistance therapy optimisation

Introduction and Epidemiology

The key features of PCOS is (i) dysfunctional insulin activity in muscle, liver and adipose tissues leading to IR and hyperinsulinaemia and (ii) intact insulin induced overproduction of androgens by theca cells in the ovarian tissue causing hyperandrogenaemia. PCOSa common endocrinopathy of complex etiology that produces symptoms in about 5-10% of women during their reproductive years [1].

Symptoms

The main symptoms of PCOS are anovulation, insulin resistance, and hyperandrogenaemia.

Anovulation

Anovulation results in irregular menstrual pattern (e.g. oligomenorrhea or amenorrhea) and infertility. The number of primordial follicles is normal in women with PCOS, while primary and secondary follicles are significantly increased. Anovulation occur because of the lack of development of a dominant follicle [2,3]. The disturbance in menstrual pattern is so common that about 85-90% of women with oligomenorrhea have been linked to PCOS, while 30-40% of women with amenorrhea have PCOS [4]. Anovulatory infertility affects about 40% of women with PCOS and approximately 90-95% of anovulatory women seeking help from infertility clinics have PCOS [2].

Insulin resistance

Researchers are still trying to unravel the fundamental defects that initiate PCOS. Studies during the recent years have revealed intracellular defective mechanisms that initiate IR. In brief, insulin binds to the insulin receptor of the muscle, liver and adipose tissue cells, but is unable to trigger the downstream intracellular pathway. Dysfunctional insulin pathways in PCOS includes impaired (i) autophosphorylation of tyrosine residues on the β subunit of insulin receptor and (ii) reduced phosphorylation and activation of phosphoinositide-3 kinase (PI3K), which leads to a reduced (a) phosphorylation and activation of protein kinase B (PKB), (b) phosphorylation and inactivation of glycogen synthase kinase-3 resulting in glycogen-synthase activation and (c) translocation of insulin-responsive glucose transporter-4 to the cell surface [5]. Hyperinsulinemia is found in about 80% of obese and 30-40% of lean women with PCOS [6].

Hyperandrogenaemia

High levels of male hormones creates hormonal imbalance and leads to hirsutism and acne, and in some cases hypermenorrhea. Hirsutism and acne features may be explained by difference in expression of 5α-reductase in the sebaceous gland and the hair follicle and resulting higher dihydrotestosterone in the hair follicle [7]. Inspite of IR at peripheral sites the ovary remains sensitive to insulin as observed in PCOS women with both normal and high BMI [8-10]. The action of insulin on the liver leads to a decrease in the production of sex hormone binding globulin and insulin-like growth factor 1 binding protein which results in an increase in unbound testosterone. Thus, although the ovary is the major site of increased androgen production in PCOS, IR itself may contribute to the overall androgen levels. In a study by Azziz et. al. 2004 the clinical features of PCOS women with androgen excess were hirsutism in 75.5% and acne in 14.2% [11].

Diagnosis

Clinical assessment of PCOS involves (i) history-taking of the patient with emphasis on menstrual pattern, acne, male hair growth, breast development, obesity and occurrence/history of PCOS in near family, (ii) gynecologic ultrasonography establishing "follicular arrest" and (iii) blood tests determining the serum levels of androgens.

In 2003 a consensus workshop sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine in Rotterdam amended the National Institutes of Health and National Institute of Child and Human Development consensus criteria to include polycystic ovaries as a third diagnostic marker and to allow for a diagnosis of PCOS if two of three criteria are met after excluding other androgen excess or related disorders, such as pituitary and adrenal dysfunction: (i) oligoovulation and/or anovulation, (ii) excess androgen activity and (iii) gynecologic ultrasound showing polycystic ovaries [12].

PCOS associated cardiovascular disease development

IR leads to endothelial- and mitochondrial- dysfunction [13], and this may lead to development of cardiovascular diseases, such as coronary atherosclerosis and coronary artery disease. A study by Dahlgren et al. showed an increased relative risk of 7.4 of developing myocardial infarction in PCOS women compared to age-matched female subjects [14]. Furthermore, activation of PI3K and PKB signalling pathways have been shown to be important risk salvage proteins in cardiovascular diseases [15], thus emphasising the role and importance of these key kinases in both IR and cardiovascular diseases.

PCOS therapy options

Management of clinical manifestations of PCOS for (i) menstrual irregularities and hirsutism includes oral contraceptives, (ii) androgen excess includes spironolactone and finasteride and (iii) infertility include clomiphene, laparoscopic ovarian drilling, gonadotropins, and assisted reproductive technology.

It is estimated that 10-20% of women with PCOS develop diabetes [16]. The effect of these drugs on reducing the IR by increasing the glucose uptake and reducing hyperandrogenaemia are not optimal, as the drugs with limited adverse effect (e.g metformin and chlomiphene) only show limited improvement in insulin sensitivity, while drugs with strong recovery of insulin sensitivity (e.g. rosiglitazone and troglitazone) have demonstrated severe adverse effects (e.g. liver failure and heart attack), and have therefore been withdrawn from the market [17]. The intracellular mechanisms involved in the manifestation of PCOS are slowly emerging including many of the physiological and cellular aspects of PCOS, however, there is a severe lack of understanding and subsequent studies designed to find optimal and specific treatment for women with PCOS and IR.

In vitro insulin resistance organ culture model

There are limits and obstacles when investigating the underlying signalling pathways of PCOS in patients, as the samples are difficult to access due to ethical restrains and the number of samples is limited. The use of relevant diabetic animal models is also problematic, as these animals suffer extremely due to their condition. Therefore, it is fundamental to develop a reliable, reproducible and easily modified model that mimics the intracellular mechanisms of PCOS IR condition. This IR organ culture model will make it possible to investigate pathways and therapeutic influence in great detail. Previous studies have shown that addition of the key risk factors for IR (high dose of insulin and glucose) to foetal rat liver and lung tissue produces a marked alteration of the underlying key cellular components involved in IR, such as glycogen synthase activity and glycogen production. These cellular alterations are observed in PCOS women and diabetic patients as well [5,18,19]. Developing an IR organ culture model in rat coronary arteries will allow investigation of altered expression of intracellular key components observed during IR and vascular (dys)function and the associated response to clinically relevant anti-diabetic treatment options and adjunct therapy. Vascular and endothelium (dys)function can be measured by wire-myograph experiments, while intracellular key components can be studied by western blot, immunohistochemistry and mRNA and microRNA real time PCR analysis (Figure 1).

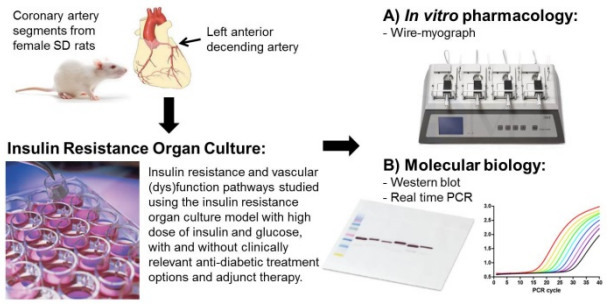

Figure 1: Overview of proposed insulin resistance organ culture model study. Left anterior decending artery segments from female sprague dawley rats will be incubated in organ culture with specific high dose of insulin and glucose, with and without clinically relevant anti-diabetic treatment options and adjunct therapy. Wire-myograph system will be used for functional studies of the vessels, while western blot and real time PCR analysis will be used for in depth molecular biology studies of key intracellular pathway components.

In addition to the IR perspective this IR organ culture model will also allow the assessment of myocardial injury or cardioprotection by measuring specific biomarkers of myocardial injury [20] and the vascular tone altered through differential expression of specific G-protein coupled receptors involved in myocardial injury development [21].

Conclusion

Development of an IR organ culture model will optimise insulin sensitivity therapy options in PCOS. The model will inform the advancement of new therapy options or modulate existing treatments with adjunct therapy, which will improve long-term outcome and life quality of women with IR due to PCOS.

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