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Female adipocyte androgen synthesis and the effects of insulin

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ABSTRACT

The metabolic syndrome is a cluster of metabolic disorders characterized by insulin resistance and hyperinsulinaemia, and its presence can increase the risk of cardiovascular disease significantly. The metabolic syndrome is associated with increased circulating androgen levels in women, which may originate from the ovaries and adrenal glands. Adipocytes are also able to synthesise steroid hormones, and this output has been hypothesised to increase with elevated insulin plasma concentrations. However, the contribution of the adipocytes to the circulating androgen levels in women with metabolic syndrome is limited and the effects of insulin are not fully understood. The aim of this study was to investigate the presence of steroid precursors and synthetic enzymes in human adipocyte biopsies as markers of possible adipocyte androgen synthesis. We examined pre and mature adipocytes taken from tissue biopsies of abdominal subcutaneous adipose tissue of participating women from the Department of Obstetrics and Gynaecology, of the Royal Derby Hospital. The results showed the potential for localised adipocyte androgen synthesis through the presence of the androgen precursor progesterone, as well as the steroid-converting enzyme 17α-hydroxylase. Furthermore, we found the controlled secretion of androstenedione *in vitro* and that insulin treatment caused levels to increase. Continued examination of a localised source of androgen production is therefore of clinical relevance due to its influence on adipocyte metabolism, its negative impact on female steroidogenic homeostasis, and the possible aggravation this may have when associated to obesity and obesity related metabolic abnormalities such as hyperinsulinaemia.

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1. Introduction

Adipose tissue plays an important role in the regulation of levels and bioactivity of sex steroids [2,7,13]. Examination into the adipocyte steroidogenic pathway involved in oestrogen conversion has shown androstenedione conversion by aromatase to estrone (E1), and that this is cytochrome P450-dependent. Changes in localised levels of these hormones may also be involved in gender-related fat deposition. Studies have detected the presence of enzymes including aromatase, 3-beta-hydroxysteroid dehydrogenase (HSD), 3-alpha-HSD, 1,1-beta-HSD, 17-beta-HSD, 7-alpha-hydroxylase, 5-alpha-reductase and UDP-glucuronosyltransferase 2B15, in adipose cells and that a correlation exists towards obesity, central fat accumulation, and the metabolic syndrome [8,9]. With the importance of obesity and the association this has with metabolic abnormalities such as insulin resistance [1], hyperinsulinemia and subsequent disorders of the cardiovascular system, examination into adipocyte function and their response to hormonal messengers is of clinical importance. Furthermore associations have been made between obesity and androgen regulation with androgens being shown to decrease plasma adiponectin, which may subsequently decrease in insulin sensitivity [32].

It is well recognised that androgens are produced in sex organs [5] and the adrenal glands [37,39,42]. However, *de novo* synthesis of sex hormones also occurs within sub-cutaneous adipocytes, which have been shown to be more steroidogenically active than visceral adipocytes. However limited studies have examined the capabilities of peripheral tissues such as skin and adipose tissue to synthesise weaker circulatory androgens. Currently 15 steroidogenic enzymes are recognised to exist within adipose tissue including aromatase, 3β-hydroxysteroid dehydrogenase [6] type 1 [8], 11β-hydroxysteroid dehydrogenase types 1 and 2 [9], 5α-reductase [10] and 17β-HSD types 2, 3 and 5. It is also recognised that adipocytes contain components necessary for transport and metabolism of cholesterol which is essential for the initial steps of steroid synthesis. Furthermore CYP11A1 has the capacity to produce pregnenolone, the precursor to progesterone and the foundation to androgen steroidogenesis. This has been demonstrated through the mitochondrial product 27-hydroxycholesterol (27HC) and by the action of CYP27A1 also now known to be present in adipocytes [28]. Based on these findings, the capacity for peripheral tissue to synthesise and inactivate androgens is feasible.

Examination of a localised source of androgen production may therefore be of clinical relevance due to its general influence on adipocyte metabolism, its negative impact in female steroidogenic homeostasis and the possible aggravation this may have when associated to obesity and obesity related metabolic abnormalities [11]. In the present study we hypothesised that the precursors and enzymes involved in the aromatisation and production of steroids within adipose tissue were suggestive of localised androgen synthesis. More specifically we attempted to support the controversial presence of CYP17 as described by Puche et al. [35] and MacKenzie et al. [29] by showing the expression of the steroid-converting enzyme 17α-hydroxylase [6,29,35], the progesterone precursor, and the controlled secretion of androstenedione *in vitro*. Our rationale was based on the androgen synthetic pathway found within ovarian steroidogenesis [17], whereby the presence of known precursors and enzymes necessary for thecal steroid metabolism in adipocytes may indicate the presence of androgen synthesis. Subcutaneous adipocyte samples were chosen based on reports of increased expression of steroidogenic enzymes compared to visceral adipocyte samples, which may suggest higher hormonal output.

2. Materials and methods

2.1. Tissue collection

Adipose tissue biopsies (~5 g) were taken from subcutaneous adipose tissue of the abdominal wall of participating women either during a planned surgical procedure or under local anaesthesia in the outpatient clinic [4] in the Department of Obstetrics and Gynaecology, of the Royal Derby Hospital. Inclusion criteria for the study consisted of women with regular menstrual cycles (28 day cycle), normal serum levels of androstenedione (0.2–2.9 nmol/l) and fasting insulin (17.8–173 pmol/l). All women were of childbearing age, ranging from 20 to 45 years with BMI < 35 kg/m^2. Exclusion criteria consisted of any metabolic or endocrine disease, such as diabetes mellitus and thyroid disease and concurrent treatment with: hormonal therapy such as hormonal contraception, progestogen therapy, thyroxin hormone or