REVIEW

The effects of androgens on metabolic functions in females

Takeshi Iwasa[1], Yuri Yamamoto[1], Akari Shinya[1], Saki Minato[1], Rie Yanagihara[1], Shuhei Kamada[1], Junki Imaizumi[1], Tomohiro Kagawa[1], Aya Shirakawa[1], Hiroki Noguchi[1], Tomotaka Nakagawa[1], Miyu Taniguchi[1], Yuri Kadota[1], Takako Kawakita[1], Kanako Yoshida[1], Takeshi Kato[1], Toshiyuki Yasui[2], and Minoru Irahara[1]

[1]*Department of Obstetrics and Gynecology, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan,* [2]*Department of Reproductive and Menopausal Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan*

Abstract : The metabolic effects of androgens and their underlying mechanisms in females have been revealed by recent studies. An excess of androgens can have adverse effects on feeding behavior and metabolic functions and induce metabolic disorders/diseases, such as obesity, insulin resistance, and diabetes, in women and experimental animals of reproductive age. Interestingly, these effects of androgens are not observed in ovariectomized animals, indicating that their effects might be dependent on the estrogen milieu. Central and peripheral mechanisms, such as alterations in the activity of hypothalamic factors, reductions in energy expenditure, skeletal muscle insulin resistance, and β-cell dysfunction, might be related to these androgens' effects. J. Med. Invest. 68 : 228-231, August, 2021

Keywords **:** *androgen, metabolic function, obesity*

INTRODUCTION

Energy balance and reproductive function are closely linked in most species (1, 2). Sex hormones, i.e. estrogens and androgens, are involved in the regulation of energy metabolism, food intake, and body weight in mammals and humans (2). Generally, estrogens prevent excess body weight gain and obesity in females of reproductive and postmenopausal ages by suppressing food intake and increasing metabolic expenditure (2-4). On the contrary, it is assumed that androgens increase the risk of metabolic dysfunctions and excess body weight in women of reproductive age, however, a cause-effect relationship remains to be established. In addition, the roles of androgens on metabolic functions in postmenopausal women are highly controversial. Some studies have reported that high testosterone level is associated with increased risk of insulin resistance and cardiovascular disease, whereas other studies have shown that circulating DHEA-S level dose not affect the risk of cardiovascular disease and mortality (5). Similarly, recent study has proposed that it is unknown whether hyperandrogenic women truly have increased risk of mortality and cardiovascular disease later in life (6). Interestingly, contrary to case in females, it has been demonstrated that androgens have favorable effects on metabolic functions in males ; i.e., androgens prevent some metabolic disorders, such as insulin resistance (IR) and obesity, in males (7).

Here, we review the available literature on the roles of androgens in metabolic functions in females of reproductive age, with special emphasis on the mechanisms that have recently been proposed to underlie these roles.

Received for publication June 22, 2021 ; accepted July 4, 2021.

Address correspondence and reprint requests to Takeshi Iwasa, Department of Obstetrics and Gynecology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-631-2630.

EFFECTS OF ANDROGENS ON METABOLIC FUNCTION IN FEMALES OF REPRODUCTIVE AGE

Effects of endogenous androgens

It has been suggested that endogenous androgens affect metabolic functions in women of reproductive age and that an excess of androgens might increase the risk of some metabolic disorders/diseases, such as visceral obesity, IR, and metabolic syndrome. Women with polycystic ovary syndrome (PCOS), frequently accompanied by a hyperandrogenic status, exhibit increased prevalence rates of type 2 diabetes and metabolic syndrome compared with women without PCOS (8, 9). Similarly, hyperandrogenic women with PCOS display higher prevalence rates of abdominal obesity, IR, and adverse metabolic profiles than women without PCOS and those with non-hyperandrogenic PCOS. These effects of a hyperandrogenic status on metabolic functions are also observed in women without PCOS. Specifically, hyperandrogenic premenopausal women with high free androgen indices (FAI) demonstrated higher waist circumference values, fasting glucose and insulin levels, systolic and diastolic blood pressure levels, and serum triglyceride levels and lower serum high-density lipoprotein-cholesterol levels (10). In addition, women with idiopathic hirsutism or PCOS displayed greater waist-hip ratios (WHR) than age- and weight-matched non-hirsute women, and the plasma testosterone level was found to be positively correlated with the WHR (11). Based on the findings of these studies regarding the relationships between hyperandrogenic status and metabolic disorders, further studies evaluated whether antiandrogenic treatment improves the metabolic status of women with PCOS. It was demonstrated that treatment with flutamide, an antiandrogenic medicine, during 12 months caused reductions in visceral and subcutaneous fat mass, lipid profile improvements, and increases in insulin sensitivity in overweight-obese women with PCOS (12).

Interestingly, some studies have suggested that androgens might affect food cravings and food preferences in young women. For example, young women with high FAI exhibited increased craving for certain foods, such as high-fat foods and fast foods (13), and women with PCOS displayed higher prevalence rates of abnormal eating behaviors, such as bulimic behavior (14). In

addition, women with bulimia nervosa tended to have higher androgen levels than normal women (15), and antiandrogenic oral contraceptive use reduced meal-related hunger and eating behavior in bulimic women (16).

Thus, endogenous androgens play roles in the regulation of metabolic functions and feeding behavior in women of reproductive age, and an excess of androgens might increase the risk of metabolic disorders/diseases.

Effects of exogenous androgens

The hypothesis that an excess of androgens is related to various metabolic disorders/diseases, has been supported by studies that evaluated the effects of exogenous androgens on metabolic functions. Androgen-treated female-to-male transsexual patients exhibited higher HOMA-IR (homeostatic model assessment of insulin resistance) values than those who did not receive hormonal treatment (17), indicating that exogenous androgens might increase IR. In addition, the administration of methyltestosterone reduced glucose uptake during insulin infusions in non-obese premenopausal women, suggesting that hyperandrogenemia induces IR (18). These phenomena can be reproduced in experimental animals via the chronic administration of androgens. The chronic (4 weeks) administration of dihydrotestosterone (DHT) increased visceral adiposity in female mice of reproductive age (19), and the administration of testosterone (around 2 weeks) increased visceral and subcutaneous fat weight and body weight in female rats of reproductive age (20, 21) (Table 1). Interestingly, such effects of androgen on fat and body weight are observed in gonadally intact or estradiol-supplemented ovariectomized rats, but not in non-supplemented ovariectomized rats (20, 21) (Table 1). Animals that were subjected to longer-term (5 to 19 weeks) androgen treatment display increased food intake and body weight gain, IR, and hyperlipidemia, as well as irregular estrous cycles and morphological ovarian changes (22-24). In addition, the chronic administration of testosterone also increased the preference of female rats of reproductive age for a high-fat diet (25), indicating that the effects of androgens on feeding behavior can also be reproduced in animal models.

Table 1. Effects of androgen administration on body weight, food intake, fat amount, and hypothalamic factors in ovariectomized with E2 administered and ovariectomized female rats.

	ovarictomy+E2	ovariectomy
Body weight	↑	↓
Food intake	→	↓
Fat amount	↑	↓
Adipocyte size	↑	↓
Hypothalamic Aromatase	→	↑
Hypothalamic androgen receptor	↓	→
Hypothalamic IL-1, TNFα	↑	↓

E2 ; estradiol, IL-1 ; interleukin-1, TNF-α ; tumor necrosis factor-α, ↑ ; increase, ↓ ; decrease

HYPOTHESES OF THE MECHANISMS OF ANDROGENS' EFFECTS

Changes in hypothalamic functions

It has been shown that an excess of androgens alters the activity and mRNA expression of some hypothalamic factors, and these alterations might be involved in the adverse effects of androgens on metabolic functions. The chronic administration of DHT reduced the hypothalamic mRNA expression of proopiomelanocortin (POMC), which is an anorectic factor, and POMC neuronal innervation into other hypothalamic regions in female mice of reproductive age (19). In addition, we observed that chronic testosterone administration reduced the hypothalamic mRNA expression of estrogen receptor-α (ER-α) and/or increased the mRNA expression of pro-inflammatory cytokines (20, 21). It has been established that the favorable effects of estrogens on metabolic functions are partly mediated by hypothalamic ER-α (2-4) and that low-grade hypothalamic inflammation undermines homeostatic responses that protect against obesity (26). Therefore, the downregulation of ER-α expression and the upregulation of pro-inflammatory cytokine expression in the hypothalamus, which were observed in our studies, might underlie androgen-induced metabolic disorders. We also found that such alterations in hypothalamic ER-α and pro-inflammatory cytokine expression, as well as increases in fat mass, occurred in gonadally intact or estradiol-supplemented ovariectomized rats, but not in ovariectomized rats (20, 21). This indicates that the effects of androgens on metabolic functions might depend on the estrogen milieu ; i.e., androgens have adverse effects on females of reproductive age, whereas their effects might be decreased or reversed in post-menopausal females and males.

Reductions in energy expenditure

It has been reported that an excess of androgens reduces energy expenditure, which is associated with visceral obesity. In female mice of reproductive age, chronic DHT administration prevented the leptin-induced activation of brown adipose tissue (BAT) thermogenesis, resulting in a reduction in energy expenditure and an increase in visceral fat mass (19). Similarly, chronic dehydroepiandrostenedione (DHEA) administration reduced BAT activity, body temperature, and O_2 consumption in female rats of reproductive age, whereas the transplantation of BAT from rats that had not been administered DHEA negated these DHEA-induced changes and normalized systemic insulin sensitivity (27). These results indicate that reductions in endogenous BAT activity are closely related to the adverse effects of androgens on metabolic functions.

Skeletal muscle insulin resistance

It has been shown that an excess of androgens can induce IR in women and female experimental animals. High testosterone levels produced IR, which was detected using the hyperglycemic and euglycemic hyperinsulinemic clamp tests, in pre-menopausal women (18, 28), and such testosterone-induced IR might mainly occur in skeletal muscle (18). The administration of testosterone also induced IR in muscles, together with reductions and increases in the relative numbers of type 1 and type 2 muscle fibers, respectively, in female rodents (29, 30). Although the detailed mechanisms by which androgens promote muscular IR remain unclear, it has been suggested that androgens might act as aggravating factors rather than as initiators of IR.

β-cell dysfunction

It has been suggested that an excess of androgens causes a predisposition towards pancreatic β-cell dysfunction by activating some β-cell stressors. Hyperandrogenic women exhibit β-cell hyperfunction, which might induce secondary β-cell dysfunction (31). In addition, excess testosterone induced β-cell dysfunction via an androgen receptor-dependent mechanism (32) in female mice, and direct androgen exposure to isolated pancreatic islets induced an impaired response to glucose stimulation (32, 33). These effects of androgens on β-cells might be caused by systemic oxidative stress, low-grade inflammation, and/or IR (32, 34).

EFFECTS OF ANDROGENS ON METABOLIC FUNCTIONS IN POSTMENOPAUSAL WOMEN

As noted above, the effects of androgens on metabolic functions in postmenopausal women are disputed. It has been reported that androgen activity is higher in postmenopausal women with impaired glucose tolerance than in normal women (35) and that high testosterone levels in postmenopausal women predict insulin resistance and the future incidence of type 2 diabetes (36). On the other hand, higher serum estradiol levels are strongly related to the pathogenesis of type 2 diabetes in postmenopausal women (37). These findings indicate that excesses of estrogen and androgens might act as risk factors for metabolic disorders in postmenopausal women. Interestingly, some data have shown that testosterone therapy has favorable effects on body composition and cardiovascular function, as well as on libido, bone, and cognitive performance (38). Thus, contrary to endogenous androgens, exogenous androgens might help to protect against metabolic disorders.

CONCLUSION

Androgens affect metabolic functions and feeding behaviors in females of reproductive age, and an excess of androgens might increase the risk of metabolic-related disorders/diseases. It can be assumed that increased consumption of high-fat diet might enhance the adverse effects of androgens on metabolic functions. Central and peripheral mechanisms are considered to contribute to these effects of androgens (Figure 1).

CONFLICT OF INTEREST

The author declares no conflicts of interest.

REFERENCES

1. Iwasa T, Matsuzaki T, Yano K, Irahara M : Effects of low energy availability on reproductive functions and their underlying neuroendocrine mechanisms. J Clin Med 7 : E166, 2018
2. Hirschberg AL : Sex hormones, appetite and eating behavior in women. Maturitas 71 : 248-256, 2012
3. Blaustein JD, Wade GN : Ovarian influences on the meal patterns of female rats. Physiol Behav 17 : 201-208, 1976
4. Asarian L, Geary N : Sex differences in the physiology of eating. Am J Regul Integr Comp Physiol 305 : R1215-R1267, 2013
5. Yasui T, Matsui S, Tani A, Kunimi K, Yamamoto S, Irahara M : Androgen in postmenopausal women. J Med Invest 59 : 12-27, 2012
6. Gunning MN, Fauser BCJM : Are women with polycystic ovary syndrome at increased cardiovascular disease risk later in life? Climacteric 20 : 222-227, 2017
7. Navarro G, Allard C, Wu W, Mauvais-Jarvis F : The role of androgens in metabolism, obesity, and diabetes in males and females. Obesity 23 : 713-719, 2015
8. Moran L, Teede H : Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod Update 15 : 477-488, 2009
9. Escobar-Morreale HF : Polycystic ovary syndrome : definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol 14 : 270-284, 2018
10. Korhonen S, Hippelainen M, Vanhala M, Heinonen S, Niskanen L : The androgenic sex hormone profile is an essential feature of metabolic syndrome in premenopausal women: a controlled community-based study. Fertil Steril 79 : 1327-1334, 2003
11. Evans DJ, Barth JH, Burke CW : Body fat topography in women with androgen excess. Int J Obes 12 : 157-162, 1988

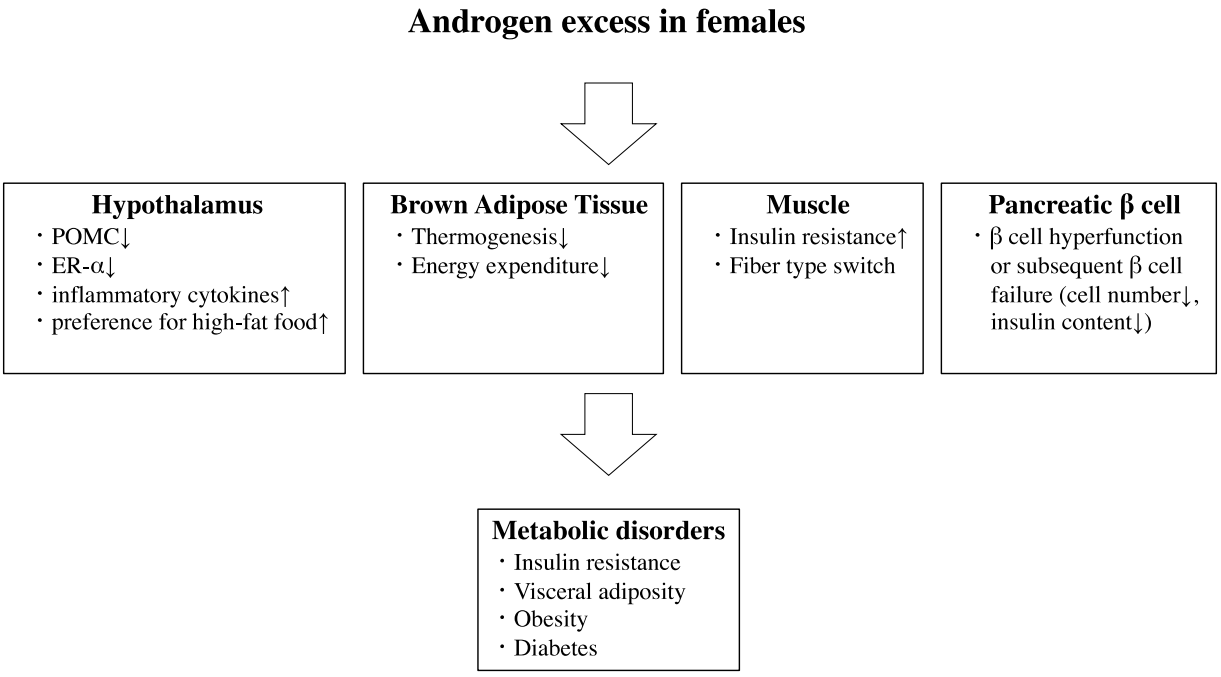

Figure 1. Effects of androgen excess on function of central and peripheral tissues in females. These androgen's effects increase the risks of some metabolic-related disorders.

12. Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, Pagotto U, Pasquali R : Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome : a randomized, 12-month, placebo-controlled study. J Clin Endocrinol Metab 91 : 3970-3980, 2006
13. Lim SS, Norman RJ, Clifton PM, Noakes M : Hyperandrogenemia, psychological distress, and food cravings in young women. Physiol Behav 98 : 276-280, 2009
14. McCluskey S, Evans C, Lacey JH, Pearce JM, Jacobs H : Polycystic ovary syndrome and bulimia. Fertil Steril 55 : 287-291, 1991
15. Sundblad C, Bergman L, Eriksson E : High levels of free testosterone in women with bulimia nervosa. Acta Psychiatr Scand 90 : 397-398, 1994
16. Naessen S, Carlstrom K, Bystrom B, Pierre Y, Hirschberg AL : Effects of an antiandrogenic oral contraceptive on appetite and eating behavior in bulimic women. Psychoneuroendocrinology 32 : 548-554, 2007
17. Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T : Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. J Sex Med 8 : 1686-1693, 2011
18. Diamond MP, Grainger D, Diamond MC, Sherwin RS, Defronzo RA : Effects of methyltestosterone on insulin secretion and sensitivity in women. J Clin Endocrinol Metab 83 : 4420-4425, 1998
19. Nohara K, Laque A, Allard C, Munzberg H, Mauvais-Jarvis F : Central mechanisms of adiposity in adult female mice with androgen excess. Obesity (Silver Spring) 22 : 1477-1484, 2014
20. Iwasa T, Matsuzaki T, Tungalagsuvd A, Munkhzaya M, Yiliyasi M, Kato T, Kuwahara A, Irahara M : Effects of chronic testosterone administration on body weight and food intake differ among pre-pubertal, gonadal-intact, and ovariectomized female rats. Behav Brain Res 309 : 35-43, 2016
21. Iwasa T, Matsuzaki T, Yano K, Yanagihara R, Tungalagsuvd A, Munkhzaya M, Mayila Y, Kuwahara A, Irahara M : The effects of chronic testosterone administration on body weight, food intake, and adipose tissue are changed by estrogen treatment in female rats. Horm Behav 93 : 53-61, 2017
22. Walters KA, Allan CM, Hndelsman DJ : Rodent models for human polycystic ovary syndrome. Biol Reprod 86 : 140, 1-12, 2012
23. Iwasa T, Matsuzaki T, Tungalagsuvd A, Munkhzaya M, Mayila Y, Kato T, Kuwahara A, Irahara M : Effects of chronic DHEA treatment on central and peripheral reproductive parameters, the onset of vaginal opening and the estrous cycle in female rats. Gynecol Endocrinol 32 : 752-755, 2016
24. Iwasa T, Matsuzaki T, Yano K, Mayila Y, Yanagihara R, Yamamoto Y, Kuwahara A, Irahara M : Prenatal undernutrition affects the phenotypes of PCOS model rats. J Endocrinol 239 : 137-151, 2018
25. Iwasa T, Matsuzaki T, Yano K, Mayila Y, Kuwahara A, Matsui S, Irahara M : Effects of chronic testosterone administration on the degree of preference for a high-fat diet and body weight in gonadal-intact and ovariectomized female rats. Behav Brain Res 349 : 102-108, 2018
26. Thaler JP, Guyenet SJ, Dorfman MD, Wisse BE, Schwartz MW : Hypothalamic inflammation: marker or mechanism of obesity pathogenesis? Diabetes 62 : 2629-2634, 2013
27. Yuan X, Hu T, Zhao H, Huang Y, Ye R, Lin J, Zhang C, Zhang H, Wei G, Zhou H, Zhao J, Wang H, Liu Q, Lee HJ, Jin W, Chen ZJ : Brown adipose tissue transplantation ameliorates polycystic ovary syndrome. Proc Natl Acad Sci USA 113 : 2708-2713, 2016
28. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ : Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 79 : 265-271, 1994
29. Holmang A, Larsson BM, Brzezinska Z, Bjorntorp P : Effects of short-term testosterone exposure on insulin sensitivity of muscles in female rats. Am J Physiol 262 : E851-E855, 1992
30. Holmang A, Svedberg J, Jennische E, Bjorntorp P : Effects of testosterone on muscle insulin sensitivity and morphology in female rats. Am J Physiol 259 : E555-E560, 1990
31. Goodarzi MO, Erickson S, Port SC, Jennrich RI, Korenman SG : Beta-cell function : a key pathological determinant in polycystic ovary syndrome. J Clin Endocrinol Metab 90 : 310-315, 2005
32. Liu S, Navarro G, Mauvais-Jarvis F : Androgen excess produces systemic oxidative stress and predisposes to beta-cell failure in female mice. PloS One 5 : e11302, 2010
33. Roland AV, Nunemaker CS, Keller SR, Moenter SM : Prenatal androgen exposure programs metabolic dysfunction in female mice. J Endocrinol 207 : 213-223, 2010
34. Gonzalez F, Rote NS, Minium J, Kirwan JP : Increased activation of nuclear factor kappaB triggers inflammation and insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 91 : 1508-1512, 2006
35. Larsson H, Ahren B : Androgen activity as a risk factor for impaired glucose tolerance in postmenopausal women. Diabetes Care 19 : 1399-1403, 1996
36. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL : Endogenous sex hormones and the development of type 2 diabetes in older men and women : the Rancho Bernardo study. Diabetes Care 25 : 55-60, 2002
37. Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S : Plasma sex steroid hormones and risk of developing type 2 diabetes in women : a prospective study. Diabetologia 50 : 2076-2084, 2007
38. Davis SR : Androgen therapy in women, beyond libido. Climacteric Suppl 1 : 18-24, 2013