Translational research

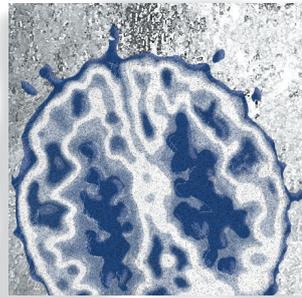# Sex differences in the effects of androgens acting in the central nervous system on metabolism

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One of the most sexually dimorphic aspects of metabolic regulation is the bidirectional modulation of glucose and energy homeostasis by testosterone in males and females. Testosterone deficiency predisposes men to metabolic dysfunction, with excess adiposity, insulin resistance, and type 2 diabetes, whereas androgen excess predisposes women to insulin resistance, adiposity, and type 2 diabetes. This review discusses how testosterone acts in the central nervous system, and especially the hypothalamus, to promote metabolic homeostasis or dysfunction in a sexually dimorphic manner. We compare the organizational actions of testosterone, which program the hypothalamic control of metabolic homeostasis during development, and the activational actions of testosterone, which affect metabolic function after puberty. We also discuss how the metabolic effect of testosterone is centrally mediated via the androgen receptor.

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Introduction

The role of sex and gender in disease is a fundamental issue in medicine. Elucidating the molecular, biochemical, and physiological determinants of these biological sex differences is a necessary step toward precision, gender-specific medicine. There are fundamental aspects of the control of metabolic homeostasis that are regulated differently in males and females and that probably influence both the development of diabetes and obesity, as well as the response to pharmacological intervention.[1] Perhaps one of the most sexually dimorphic aspects of metabolic regulation is the bidirectional modulation of glucose and energy homeostasis by the male hormone testosterone in males and females.[2] Indeed, testosterone deficiency predisposes men to obesity, metabolic syndrome, and type 2 diabetes (T2D).[2-5] In contrast, testosterone excess predisposes women to obesity and T2D.[2,5,6] Considering that men with androgen deficiency and women with androgen excess represent a large segment of the population, it is vital to understand the determinants of sex differences in testosterone's effects on metabolism.[3,4,6] This review will discuss how androgens act in the central nervous system (CNS) to impact metabolism in a sexually dimorphic manner in males and females.

Causes of sex differences in physiology

Perinatal programming by testosterone

Extensive evidence relates sexually dimorphic aspects of physiology to brain masculinization by the testicular

Selected abbreviations and acronyms

AR	*androgen receptor*
ARC	*arcuate nucleus*
CNS	*central nervous system*
DHT	*dihydrotestosterone*
DMH	*dorsomedial hypothalamus*
ER	*estrogen receptor*
PCOS	*polycystic ovarian syndrome*
POMC	*proopiomelanocortin*
T2D	*type 2 diabetes*
VMH	*ventromedial hypothalamus*

perinatal testosterone surges in males.[7-10] Hypothalamic structure and function are modified by testosterone, leading to sex differences in reproductive behavior and physiology.[10]

The organizational-activational hypothesis of hormone action in the nervous system has gathered substantial attention since the publication of the seminal paper by Phoenix et al.[11,12] These authors demonstrated that prenatal testosterone exposure in female rodents reduced the ability of estrogen administered in adulthood to elicit female mating behavior. This paper set the framework for the organizational-activational hypothesis, which states that: (i) organizing actions of testosterone occur during a critical period of development in which testosterone acts on the brain to cause permanent changes that persist in the absence of hormone, in effect programming the brain to be masculinized (and defeminized); and (ii) activational actions of testosterone occur after puberty when the hormone acts transiently and reversibly on circuitry that has already been established.[12,13]

The idea that there is a critical period in which testosterone exerts organizing effects is key to the organizational-activational hypothesis.[12,13] Testosterone exposure must occur during this critical period for the brain to be masculinized. In human and nonhuman primate fetuses, the testicular testosterone surge occurs during the second trimester of pregnancy, which coincides with the development of the hypothalamus, the brain region that regulates both reproduction and metabolism.[14,15] In rodents, the testicular testosterone surge occurs in the first week of neonatal life, which coincides with the development of the hypothalamus.[16,17] During this critical period, testicular testosterone is capable of masculinizing the brain in males, and exogenous testosterone is capable of masculinizing the brain in females.[7,10]

In the brain, testosterone can be converted via aromatase to estradiol, which exerts its actions via estrogen receptors (ERs), or via 5α-reductase to dihydrotestosterone (DHT), which exerts its effects via androgen receptors (ARs).[18] Theoretically, either of these hormones could be responsible for the effects of testosterone on brain masculinization because both of these enzymes are expressed in the developing brain.[18] However, neonatal estradiol exposure is sufficient to masculinize the brain and elicit male-typical behavior in rodents.[7] Moreover, male mice with CNS-specific AR deficiency retain male behavior, but the frequency is reduced.[19,20] This suggests that the brain is organized to perform male behavior in the absence of AR but that AR is required to activate male behavior.

Although the available evidence clearly demonstrates that AR is not necessary for organizational effects on behavior in rodents, this is not the case in primates. Prenatal administration of DHT to female rhesus macaques during the critical period programs more male behavior in offspring.[21] Similarly, prenatal exposure to DHT programs less female sexual behavior in female macaques.[22] This is consistent with the observation of men with complete androgen insensitivity syndrome who have nonfunctional ARs but normal-to-high testosterone levels.[23] These individuals often identify as females and display female-typical behaviors. Also in contrast to rodents, estrogen appears not to play a role in the masculinization of behavior in humans because men with aromatase deficiency or ER mutation show normal male-typical behaviors and gender identity.[24] In females, the polycystic ovarian syndrome (PCOS) is an endocrine disorder characterized by androgen excess throughout life, including prenatally.[25,26,27] Lesbian women have a significantly higher prevalence of PCOS than heterosexual women, suggesting that prenatal androgen exposure programs male-typical sexual preferences.[28] Together, these results suggest that, unlike in rodents, estradiol is not necessary for the organizational effects of testosterone and that AR is responsible for brain masculinization in primates, including humans. The role of central AR in masculinizing the brain with respect to metabolism will be discussed below.

Sex hormones after puberty

Recent evidence suggests that puberty may constitute an additional critical period in which sex hormones can

exert organizational effects on the brain.[29] However, discussion of such is beyond the scope of this review. After puberty, hormones exert purely activational effects. AR is clearly required for the activation of male-typical behaviors in rodents because male mice with CNS-specific AR deficiency exhibit a reduction in the frequency of these behaviors.[19,20] In addition, testosterone can activate aggressive behavior in adult female mice, although not to the same levels as testosterone in castrated males.[30] This suggests that the AR is required for activation of male-typical behavior in both males and females. The role of central AR activation in metabolism in adults will be discussed below.

Sex chromosomes

In addition to activational and organizational effects of hormones, sex differences in physiology can result from differences in sex chromosomes. The most obvious is the sex-determining region Y (SRY) gene on the Y chromosome, which codes the testis-determining factor and is responsible for the development of the testis and the production of testosterone.[9] In addition, the gene for the AR is located on the X chromosome.[19,20] Males with Klinefelter syndrome, who have an extra X chromosome, show excess abdominal adiposity and have an increased risk of T2D, suggesting that the additional X chromosome promotes metabolic dysfunction.[31,32]

In rodents, the "four core genotypes" model has been developed to differentiate the impact of gonadal sex and sex chromosomes on physiology. This model consists of XX and XY males and females. To generate these mice, the SRY gene was removed from the Y chromosome to generate XY females. To generate XX males, the SRY gene was inserted onto an autosomal chromosome. This model shows that XX animals, regardless of gonadal sex, have increased fasting insulin, increased insulin resistance, increased liver triglycerides, increased levels of fatty acid oxidation enzymes, and increased fat mass when exposed to a high-fat diet.[33] These results are in agreement with observational data from patients with Klinefelter syndrome, suggesting that the X chromosome may impair metabolic function. Interestingly, the same group showed that XY animals on a chow diet show increased fat mass and impaired glucose tolerance relative to XX animals.[34] These results suggest that the X chromosome may only contribute to impaired metabolism in conditions of nutrient excess.

Androgen developmental programming of the CNS and the resulting sex differences in metabolism

Sex differences in neural circuitry

Differences in neural circuitry between males and females are mainly an issue of quantity and not connectivity.[10] Males and females display the same connections between the same regions, but it is the strength of these connections that differs. Within the hypothalamus, the anteroventral periventricular nucleus (AVPV) sends descending projections to the arcuate nucleus (ARC), and these descending projections are more pronounced in females.[35] These neurons are responsible for controlling gonadotropin-releasing hormone release and, thus, luteinizing hormone release. The fact that these connections are more robust in the female brain makes sense functionally because females have a greater luteinizing hormone response to estradiol than males.[36] Conversely, descending projections within the hypothalamus from the medial preoptic nucleus (MPN) to the ventromedial hypothalamus (VMH), are more robust in males.[10] This pathway may be involved in the initiation of male sexual behavior.[10] The anterior olfactory bulb sends projections to the medial amygdala and bed nucleus of the striata terminalis (BNST), which both project to several hypothalamic nuclei. This pathway is involved in pheromone sensing and is more robust in males.[10] Projections from the BNST to the AVPV are also much more robust in males than females.[37] Although the role of these projections is unknown, the authors hypothesize that they may be involved in olfaction.[37] Apart from reproduction and sexual behavior, the hypothalamus is also a key area for the control of energy balance and glucose homeostasis.[38] Therefore, the striking sex differences in hypothalamic neural circuitry described above suggest that similar sex differences in the hypothalamic circuitry controlling glucose and energy homeostasis exist.

Sex differences in AR expression in the brain

Many of the regions described above that show sexually dimorphic circuitry also express the AR, suggesting that AR may be involved in programming the sexual dimorphism of this circuitry. AR is expressed in the AVPV, ARC, and VMH of both males and females with similar levels of expression.[39-41] AR is also expressed in

the MPN and BNST, with expression levels being higher in males.[19,39-42] Other sites of AR expression include the lateral septum, medial amygdala, and premamillary nucleus.[39-42] All of these nuclei are sexually dimorphic.[10] One study reported AR expression in the suprachiasmatic nucleus, paraventricular nucleus (PVN), lateral hypothalamus, and dorsomedial hypothalamus (DMH) in males, with no expression in females.[43] This is probably due to the poor quality of the AR antibody used. In the brain stem, there is also low AR expression in the parabrachial nucleus and the nucleus of the tractus solitarius (NTS) of males, both of which are involved in metabolism.[39,44,45] Perinatal exposure to testosterone or estradiol masculinizes the MPN and BNST by increasing AR expression in these nuclei.[20] Therefore, AR expression appears to result from the organizational effects of estradiol. However, DHT treatment in adult gonadectomized males and females restores AR expression to intact male levels.[40] Together, these results suggest that in rodents, estrogens can program AR expression, whereas androgens can activate AR expression.

In humans, there is a positive correlation between testosterone levels and gray matter volume in the parahippocampus, putamen, amygdala, and occipital and insular cortices.[46] Additionally, men tend to have larger amygdala volumes, whereas females tend to have larger hippocampal volumes.[47] Both of these regions show strong AR expression in rodents.[39]

Thus, the association between sex differences in hypothalamic neurocircuitry and sex differences in hypothalamic AR expression suggests that androgen acting on AR in these hypothalamic areas may differentially affect metabolic function in males and females. Indeed, many of these regions that show sexually dimorphic expression of the AR are also involved in metabolic homeostasis, which will later be discussed in detail.[43]

Sex differences in androgen perinatal CNS programming of metabolism

Several rodent, sheep, and primate models have been used to show that perinatal androgen exposure in females programs metabolic dysfunction with adiposity and insulin resistance in adult offspring.[48-53] This is consistent with the observation that women with prenatal androgen excess, because of adrenal hyperplasia or virilizing tumors, develop central obesity and insulin resistance as adults despite normalization of androgen excess with treatment.[54,55] However, it is unclear if these effects are due to androgen acting in the CNS or elsewhere. Nevertheless, there is extensive evidence that prenatal androgen excess alters metabolism via central actions. PCOS, for example, is characterized by hyperandrogenemia and ovarian dysfunction.[25] In a rat model of PCOS in which rats are exposed to androgen excess perinatally, an enhanced sympathetic activity is observed in adulthood that precedes the development of ovarian cysts, suggesting that increased sympathetic outflow was a result of androgen programming the CNS during the perinatal period.[56] This enhanced sympathetic activity could also contribute to the development of obesity.[57] Indeed, perinatal testosterone exposure in female mice increases fat mass in adulthood.[52] This is accompanied by increased norepinephrine turnover in white adipose tissue, a marker of increased sympathetic activity.[52] These results suggest that enhanced sympathetic activity caused by central testosterone action predisposes females to the development of obesity.[58] However, it is not known whether testosterone programmed sympathetic outflow via the AR after conversion to DHT or via ERs after conversion to estradiol. Indeed, in rodents, neonatal estradiol exposure increases adiposity in adult female offspring, whereas neonatal DHT exposure does not.[53] Instead, neonatal DHT exposure increases food intake in adult female offspring, which is accompanied by a decrease in hypothalamic expression of proopiomelanocortin (POMC), an anorexigenic peptide, and a decreased intensity of neuronal projections from POMC neurons within the ARC.[53] This is essentially a masculinization of the female hypothalamic melanocortin system regarding feeding behavior, as females exposed to DHT exhibit levels of food intake, POMC expression, and POMC neuron projections similar to those of littermate control males.[53] Thus, in mice, perinatal AR activation appears to be sufficient to program the hypothalamic melanocortin system toward male-like feeding behavior. In humans, females from opposite sex twin pairs exposed to prenatal testosterone from testis of a male co-twin also develop masculinized eating behaviors as adults.[59] However, in humans, it is unknown if this is mediated via AR or ER action. Thus, testosterone seems to play a role in the programming of the brain with respect to energy intake in both rodents and humans. However, in humans, it is unknown if this is mediated via AR or ER actions. The developmental effects of testosterone in females are summarized in *Figure 1*.

Interestingly, in male offspring, perinatal testosterone excess decreases food intake, the opposite of what is seen in littermate females.[60] Paradoxically, this decrease in food intake is accompanied by a compensatory, but inefficient, increase in the hypothalamic expression of the orexigenic peptides neuropeptide Y (NPY), agouti-related peptide (AgRP), and orexin.[60] These mice also display a secondary decrease in energy expenditure that favors adiposity, which is probably the result of increased hypothalamic expression of the orexigenic peptides.[60-62] This sex difference in the programming effect of neonatal testosterone in littermate male and female metabolic homeostasis underscores the potential for sex differences in metabolic diseases arising from the complements of sex-linked genes outside the testis-determining gene SRY.[60]

Sex differences in metabolism due to androgen action in the CNS during adulthood

In men, testosterone deficiency is associated with increased visceral obesity, insulin resistance, and an increased risk of T2D.[1-5,63] Accordingly, male mice lacking AR develop obesity, insulin resistance, and glucose intolerance with aging.[64,65] Testosterone deficiency is probably causative in the development of T2D, as men on androgen-deprivation therapy for the treatment of prostate cancer are more likely to develop T2D.[63,66,67] Evidence demonstrates that in males, testosterone maintains glucose homeostasis via action on AR in muscle, liver, and pancreatic β-cells.[1,68] The question is whether testosterone acts in the male brain to maintain energy and glucose homeostasis and whether testosterone actions that favor metabolic homeostasis in males are mediated via AR or ERs. Testosterone action is probably mediated at least in part via the AR, as men that have AR variants with low transcriptional activity exhibit hyperinsulinemia and obesity.[69] However, ERs are also involved in testosterone's metabolic effect in men, as treatment with an aromatase inhibitor blocked the ability of testosterone replacement to suppress adiposity in men.[70] More direct evidence for the role of the AR in metabolic homeostasis can be gathered from androgen-receptor knockout (ARKO) mouse models. However, in many of these models, AR is deleted developmentally, making it hard to differentiate the organizational effects from the activational effects of androgen.

Male mice with global AR deficiency exhibit late-onset obesity caused by decreased energy expenditure.[64] In addition, male mice with global AR deficiency exhibit resistance to centrally administered leptin, providing indirect evidence that brain AR may also be involved in ARKO-induced leptin resistance.[43] Indeed, leptin fails to activate signal transducer and activator of transcription 3 (STAT3) in ARC neurons of male ARKO mice and does not reduce food intake or body weight.[43] The authors suggest a number of hypothalamic sites that express both AR and the leptin receptor where androgen may be acting to cause leptin resistance. These sites include the ARC, VMH, DMH, PVN, lateral hypothalamus, premamillary nucleus, and suprachiasmatic nucleus.[43] Central loss of AR function is instrumental in this phenotype, as selective neuronal AR deficiency also causes late-onset obesity in male mice.[71]

Furthermore, global AR deficiency in male mice produces glucose intolerance, insulin resistance, and increased lipogenesis.[65] CNS-specific AR deficiency
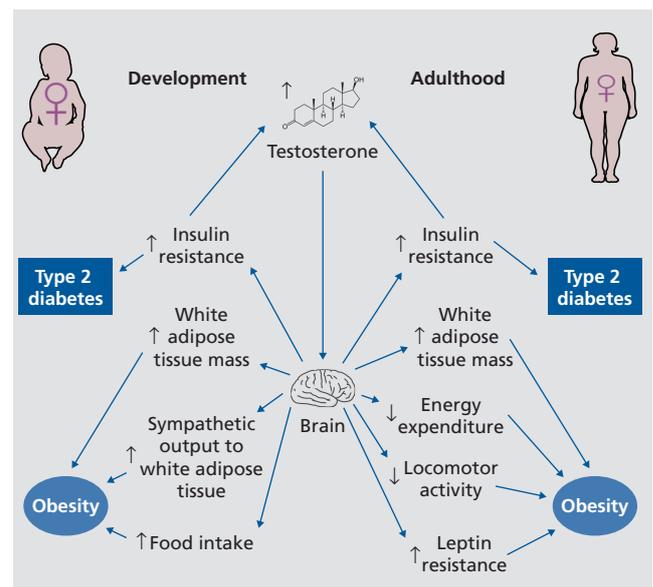

Figure 1. Testosterone excess predisposes females to type 2 diabetes and obesity. During development and adulthood, excess testosterone acts in neurons of the central nervous system to increase adiposity and insulin resistance, which predisposes females to obesity and type 2 diabetes. During development, testosterone excess may predispose to obesity by increasing sympathetic output to white adipose tissue and increasing food intake. During adulthood, testosterone excess may predispose to obesity by decreasing energy expenditure and locomotor activity, as well as increasing leptin resistance.

produces insulin resistance, glucose intolerance, and obesity on a chow diet in aging male mice.[71] These mice exhibit hypothalamic insulin resistance with enhanced nuclear factor-κB activation leading to upregulation of protein-tyrosine phosphatase 1B (PTP1B), an inhibitor of insulin signaling.[71] This hypothalamic insulin resistance results in excess expression of the orexigenic peptide AgRP, which probably mediates the effects on obesity, insulin resistance, and glucose intolerance.[71] Clearly, hypothalamic AR action confers protection against obesity and diabetes in males, at least in part by maintaining insulin action in the hypothalamus. However, it is uncertain if the effects of AR in the brain are due to organizational or activational effects, as AR deletion may lead to developmental defects that are revealed in adulthood. The central effects of testosterone deficiency in men are summarized in *Figure 2*.

However, excess AR activation can also impair metabolism in males. For example, testosterone administration to castrated rats at physiological doses improves insulin sensitivity; high doses of testosterone do not.[72] Perhaps the relationship between androgen levels is parabolic, with both low levels and very high levels causing metabolic dysfunction. This curve would be shifted far to the right in males compared with females.

In women, testosterone excess increases the risk of developing T2D.[2,5,6,73] Testosterone levels in women are positively correlated with insulin resistance and impairment of glucose tolerance.[6,73,74] PCOS is an endocrine
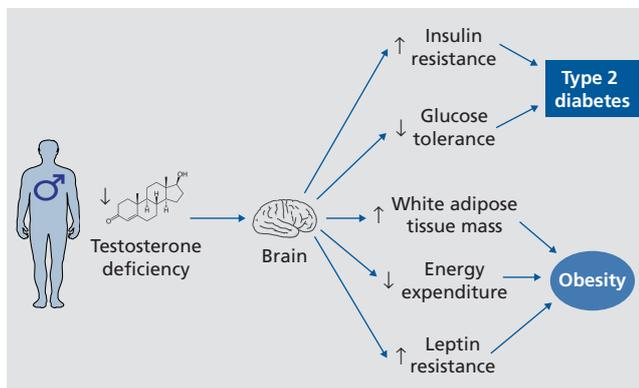

Figure 2. Testosterone deficiency predisposes males to type 2 diabetes and obesity. Testosterone deficiency predisposes men to obesity via loss of testosterone action in neurons of the central nervous system, which decreases energy expenditure and increases leptin resistance. This also predisposes to type 2 diabetes by producing late-onset insulin resistance and impaired glucose tolerance.

disorder affecting 7% of women and characterized by androgen excess throughout life.[75] In the United States, 80% of women with PCOS are obese.[75] Many women with PCOS, including lean individuals, are insulin resistant and glucose intolerant.[74,76-78] In fact, androgen levels in women with PCOS are positively correlated with insulin resistance.[74] Moreover, female to male transsexuals (with high testosterone levels) exhibit insulin resistance, suggesting a causal relationship between androgen excess and insulin resistance in women.[79] This also suggests that androgens exert activational effects to cause metabolic dysfunction in women, as androgens are administered during adulthood.[79] In addition, insulin resistance in hyperandrogenemic women can be partially reversed by antiandrogen treatment, suggesting a causal role of hyperandrogenemia on insulin resistance.[76]

Studies in animal models suggest that androgen excess in these women impairs metabolism via both organizational and activational effects, as both perinatal and adult androgen excess induce metabolic dysfunction in animal models.[48-53,80]

In female mice with chronic androgen excess during adulthood, leptin fails to reduce body weight, leading to obesity. This is paralleled by a failure of leptin to upregulate brown adipose tissue (BAT) expression of the thermogenic uncoupling protein 1 (UCP-1), which is associated with decreased energy expenditure.[80] These results suggest that there is a disruption in neural communication between the central leptin signal and BAT. In these mice, androgen excess decreased hypothalamic POMC messenger RNA expression. Interestingly, androgen excess increased POMC intensity in neuronal bodies of the ARC while simultaneously decreasing the intensity of POMC projections to the DMH, suggesting that axonal transport of POMC from the soma to the nerve terminals was impaired. As leptin action in the DMH increases sympathetic tone to BAT and increases thermogenesis, these results suggest that in mice, androgen excess decreases energy expenditure via an alteration of the melanocortin pathway to the DMH.[80,81] In female mice, androgen excess produced no alterations in food intake or leptin's anorectic action.[80] Similar to the female mouse model of androgen excess, deletion of the leptin receptor from POMC neurons leads to decreased POMC expression and increased fat mass without altering food intake.[82] Moreover, female rats exposed to androgen excess during adulthood showed reduced locomotor activity, suggesting that decreased locomotor

activity may also be contributing to the obesity seen in females exposed to chronic androgen excess.[83] The exact site of androgen action on AR that leads to this phenotype is unknown. A previous study found that only 3% of POMC neurons express AR,[84] although there is robust expression in other ARC neurons,[39-40] suggesting that the alteration in POMC neurons is indirect.

Androgen excess in females also alters glucose homeostasis. Administration of DHT to adult female mice leads to insulin resistance and glucose intolerance.[2] This effect is not observed in β-cell ARKO mice, suggesting that it is β-cell AR that is responsible for the metabolic dysfunction induced by androgen excess.[2,85,86] Our lab is currently exploring if neuronal AR also contributes to androgen excess–induced metabolic dysfunction. The central effects of testosterone excess in adult females are summarized in *Figure 1*.

Interestingly, androgen signaling could be important for proper metabolic function in females. Female global ARKO mice display normal metabolic phenotypes on a chow diet, yet they develop insulin resistance, glucose intolerance, and obesity when on a high-fat diet relative to normal mice on a high-fat diet.[87] However, the authors did not explore if this obesity was due to increased food intake or decreased energy expenditure. It is also unclear if the phenotype is due to AR in the CNS and if the effects of androgen are organizational or activational. Our lab is currently exploring if these effects are mediated by central AR.

Potential sites of androgen action in CNS on glucose and energy homeostasis

There are several regions of the brain that regulate glucose and energy homeostasis and also express AR.[39-42] Only the most likely regions for androgen action on metabolism will be discussed here.

Women with PCOS exhibit increased gonadotropin-releasing hormone (GnRH) pulsatility, suggesting impairment of hypothalamic GnRH neurons.[88] It is proposed that androgen activation of AR in ARC γ-aminobutyric acid (GABA)ergic neurons upstream of GnRH neurons downregulates the progesterone receptor, whose activity leads to suppression of GnRH pulsatility.[88] Perhaps AR action in these ARC neurons also contributes to metabolic dysfunction. The studies described above suggest that the ARC is a probable site at which androgen is acting to impact metabolism.[43,53,60,71]

Indeed, in mice, impairment of GABAergic signaling within the ARC reduces energy expenditure by reducing thermogenesis without altering food intake, a phenotype similar to that of the model of adult androgen excess in female mice.[80,89] Additionally, androgen could target the ARC in females to induce leptin resistance and hepatic insulin resistance in female mice. Indeed, several mouse models implicate insulin or leptin receptors in POMC neurons of the ARC in hepatic glucose production and the prevention of hepatic insulin resistance.[90-93]

The VMH is another site of AR expression that could mediate androgen action on metabolic regulation.[39,40] Early studies showed that lesions of the VMH, which also encompassed part of the ARC, produced hyperinsulinemia that was blocked by vagotomy, suggesting that the VMH is involved in control of glucose homeostasis via autonomic output.[94,95] More recent studies have revealed that pharmacological and genetic manipulations of the VMH in mice alter insulin sensitivity.[96,97] In contrast to the ARC, the VMH influences insulin sensitivity by controlling glucose uptake in skeletal muscle.[97,98] In addition, the VMH lesions discussed above also produced obesity independent of food intake.[95] Other early studies showed that electrical stimulation of the VMH enhanced BAT thermogenesis, suggesting that the VMH regulates energy expenditure.[99] In fact, VMH-specific deletion of forkhead box O1 (FOXO1) reduced fat mass by increasing energy expenditure, supporting the conclusion that the VMH is also involved in regulating energy expenditure and fat mass.[97]

As discussed above, the DMH is a key nucleus that regulates BAT thermogenesis and energy expenditure and could be a target of androgen action.[81,100] Indeed, in female mice exposed to chronic androgen excess, we see reduced intensity of POMC fibers in the DMH and a reduced decrease in body weight in response to the melanocortin receptor agonist, melanotan II.[80]

Conclusion

The studies reviewed here demonstrate that testosterone acts in the CNS to differentially impact glucose homeostasis and energy balance in males and females. In males, loss of central AR action (as can be observed during testosterone deficiency) decreases energy expenditure and predisposes to adiposity and insulin re-

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sistance. In females, androgen excess during the perinatal period or adulthood (as can be observed in PCOS) negatively impacts metabolic homeostasis. Perinatal androgen excess most likely involves central AR, as we observe alterations in the hypothalamic melanocortin system. Nevertheless, more studies are needed to determine the exact hypothalamic sites and mechanisms of androgen action that promote metabolic homeostasis or metabolic dysfunction during male androgen deficiency and female androgen excess. Additional studies are also needed to characterize the role of AR in female metabolic homeostasis. ❏

Conflict of Interest: The authors declare no conflict of interest.

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