Receptors & Clinical Investigation 2015; 2: e785. doi: 10.14800/rci.785; © 2015 by Naoki Harada, *et al*.
http://www.smartscitech.com/index.php/rci

REVIEW

Competitive and compensatory effects of androgen signaling and glucocorticoid signaling

Naoki Harada[1], Hiroshi Inui[2], Ryoichi Yamaji[1]

[1]*Division of Applied Life Sciences, Graduate School of Life and Environmental Sciences, Osaka Prefecture University, Sakai, Osaka 5998531, Japan*
[2]*Department of Clinical Nutrition, Graduate School of Comprehensive Rehabilitation, Osaka Prefecture University, Habikino, Osaka 5830872, Japan*

Correspondence: Naoki Harada
E-mail: harada@biochem.osakafu-u.ac.jp
Received: April 28, 2015
Published online: June 10, 2015

Androgens and glucocorticoids have competitive and compensatory effects in several physiological and pathophysiological processes. Although blood androgen levels affect blood glucocorticoid levels and vice versa, it does not fully explain the relationship between the effects of androgens and glucocorticoids. Androgens and glucocorticoids exert their functions through binding to androgen receptor (AR) and glucocorticoid receptor (GR), respectively. AR homodimer and GR homodimer bind to the androgen response element (ARE) and glucocorticoid response element (GRE), respectively, where they positively or negatively regulate transcription. AR/GR heterodimer can also form but whether it has a physiological role is unclear. Notably, some ARE/GRE sites are recognized by both AR and GR. This review focuses on the functional interventions between androgen signaling and glucocorticoid signaling in target cells that are involved in muscle atrophy, lipid metabolism in adipocytes and hepatocytes, and pancreatic β-cell death. Androgens and glucocorticoids exert opposite effects by differentially regulating key genes (*e.g.*, insulin-like growth factor-1, atrogin-1, and thioredoxin-interacting protein) involved in these physiological processes. We also review functional compensation between these steroids in the development of castration-resistant prostate cancer in which glucocorticoids compensate for the castration-induced loss of AR function by activating key genes (*e.g.*, serum/glucocorticoid-regulated kinase 1). The gene expressions regulated by androgens and glucocorticoids are regulated through at least three different mechanisms in target cells: (i) regulation of applicable ligand levels by modulation of steroid metabolite enzyme levels, (ii) regulation of each other's receptor levels, and (iii) competitive binding between AR and GR on ARE/GRE sites. Recent findings shed light on the complicated relationship between androgen signaling and glucocorticoid signaling in various cellular processes.

Keywords: androgen receptor; glucocorticoid receptor; insulin-like growth factor-1; atrogin-1; thioredoxin-interacting protein; serum/glucocorticoid-regulated kinase 1; competition; compensation

To cite this article: Naoki Harada, *et al*. Competitive and compensatory effects of androgen signaling and glucocorticoid signaling. Receptor Clin Invest 2015; 2: e785. doi: 10.14800/rci.785.

Introduction

Androgens such as testosterone and dihydrotestosterone (DHT) play pivotal roles in the development and maintenance of male reproductive organs and also play roles in carbohydrate, protein, lipid metabolisms in various tissues [1-3]. Androgenic actions of these steroid hormones are involved in masculinization, and their anabolic effects are associated with increases of muscle mass and bone mass [1-3]. Glucocorticoids such as cortisol, corticosterone, and

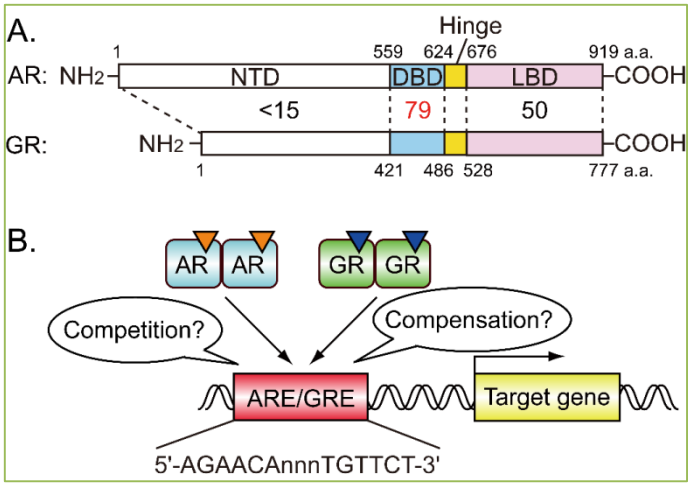

Figure 1. Domain structure and function of AR and GR. A. Schematic diagram showing domain homology (% identity) between human AR (GenBank accession No. AAA51729) and human GR (GenBank accession No. NP_000167). Steroid hormone receptors consist of an N-terminal domain (NTD), a DNA-binding domain (DBD), a hinge region, and a ligand-binding domain (LBD). **B.** Function of AR and GR as ligand-dependent transcription factor.

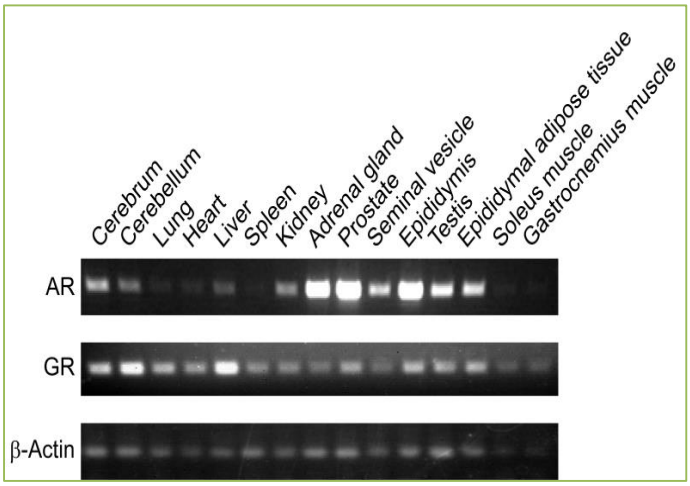

Figure 2. Tissue distributions of AR and GR in rat. Expressions of AR and β-actin are reprinted with permission [23]. For determining GR expression, cDNA was prepared as described [23] and was amplified using primers (sense: 5′-CACCCATGATCCTGTCAGTG-3′ and antisense: 5′-AAAGCCTCCCTCTGCTAACC-3′) and Ampli*Taq* Gold 360 (Applied Biosystems, Foster City, CA, USA) with annealing temperature at 58 ºC for 35 cycles.

dexamethasone (DEX, a synthetic glucocorticoid) exert anti-inflammatory and immunosuppressive effects and are involved in the metabolism of carbohydrates, proteins, and lipids [4, 5]. Catabolic actions of glucocorticoids are related to muscle atrophy and osteoporosis [6-8]. Thus, androgens and glucocorticoids have specific effects and some opposite effects [8, 9]. Administration of DEX reduces blood testosterone [10], whereas administration of testosterone increases blood corticosterone [11]. Therefore, the opposite effects of these steroids cannot be simply explained by their influence on each other's blood levels.

Androgen receptor (AR) and glucocorticoid receptor (GR), in the form of homodimers, mediate the physiological functions of androgens and glucocorticoids, respectively. AR and GR are members of the steroid hormone receptor superfamily, whose members act as ligand-dependent transcription factors [12]. Steroid hormone receptors function not only as ligand-dependent transcriptional activators [13] but also as ligand-dependent transcriptional repressors [14, 15] by recruiting co-regulators. Transcriptional initiation is achieved by recruiting co-activators that modify chromatin structure and link the basal transcriptional apparatus to the receptors [13]. On the other hand, transcriptional termination and transcriptional repression are achieved by recruiting co-repressors [16, 17]. Steroid hormone receptors are composed of a variable N-terminal domain (NTD), a highly conserved DNA-binding domain (DBD), a hinge region, and a moderately conserved ligand-binding domain (LBD) at the carboxyl-terminus [18] (Fig. 1A). The receptors can homodimerize through a D-box region in the DBD in a ligand-dependent manner [19]. The homologies of the DBD and the LBD between AR and GR are 79% and 50%, respectively. Notably, AR and GR bind to the same *cis*-element, called androgen-response element/glucocorticoid response element (ARE/GRE; 5′-AGAACAnnnTGTTCT-3′) [20, 21], whereas there also exists an AR-selective ARE (5′-AGAACAnnnAGAACA-3′) [20, 21]. AR and GR mediate fundamentally different physiological functions of androgens and glucocorticoids through activating or repressing their target gene expressions (Fig. 1B). The tissue distributions of AR and GR are at least partially responsible for determining their target gene specificities [22]. In rats, AR is mainly expressed in the adrenal gland and reproductive tissues [23] whereas GR is expressed ubiquitously (Fig. 2). The specificities of AR and GR also depend on cooperation with other transcription factors (*i.e.*, sequences surrounding the ARE/GRE), recruitment of different co-regulatory complexes, and chromatin accessibility [13, 14, 24-27]. On the other hand, the expressions of some genes such as prostate-specific antigen (PSA) and serum/glucocorticoid-regulated kinase 1 (SGK1) are induced by both AR and GR [28, 29]. It has become increasingly apparent that competitive and compensatory effects between androgens and glucocorticoids in physiological and pathophysiological processes are at least partly exerted through binding of their receptors to the common ARE/GRE sites [30, 31]. This review focuses on the competitive and compensatory effects between androgens and glucocorticoids in various cellular processes.

Competitive effects between androgen and glucocorticoid in cell physiology

Regulation of muscle mass

Skeletal muscle atrophy occurs in response to a variety conditions, such as sepsis, cachexia, starvation, denervation, and glucocorticoid treatment [32]. Glucocorticoids induce muscle atrophy, especially in fast-twitch fibers [7, 8]. Skeletal muscle mass is governed by the balance between synthesis and degradation of muscle proteins. The ubiquitin-proteasome system and the insulin-like growth factor-1 (IGF-1) signal contribute critically to protein degradation and protein synthesis, respectively, in muscle [33, 34]. Glucocorticoids increase the expressions of several atrophy-related genes, the so-called atrogenes (*e.g.*, atrogin-1, MuRF1, and forkhead box O1 (FOXO1)) and decrease the expression of IGF-1 [7, 8]. Increasing the level of atrogen-1 or MuRF1, which are muscle-specific E3 ubiquitin ligases, enhances the degradation of target proteins with the ubiquitin-proteasome system, leading to the loss of muscle mass [8, 32]. Because FOXO1 up-regulates the expressions of atrogin-1 and MuRF1 [33, 34], these atrogenes act in a coordinated manner during muscle atrophy. In contrast, IGF-1 activates IGF-1 receptor/PI3K/Akt/mTOR signaling, and consequently promotes protein synthesis [33, 34]. In addition, IGF-1 signaling phosphorylates Akt and down-regulates the transcriptional activation of FOXO1 [33, 34]. Therefore, a decrease of IGF-1 results in both decreased protein synthesis and increased protein degradation. In contrast to glucocorticoids, androgens moderately increase muscle mass and strength in hypogonadal men [35] by decreasing the expression of atrogin-1 and MuRF1 and by increasing the expression of IGF-1 in muscle [36]. Furthermore, androgens repress muscle atrophy induced by glucocorticoids [9, 37-40]. Androgens abolish the glucocorticoid-induced increase of atrogin-1, MuRF1, and FOXO1 and the glucocorticoid-induced decrease of IGF-1 in muscle [37, 38, 40]. Interestingly, androgens and glucocorticoids decrease the expression of GR and AR, respectively [10, 36]. Although it is not clear whether these steroids directly affect each other's receptor in muscular cells, glucocorticoid signaling at least partly interferes with AR expression, and androgen signaling at least partly interferes with GR expression in muscle *in vivo*. On the other hand, the regulation of atrogin-1 and IGF-1 levels by androgens and glucocorticoids are also observed in cultured myoblasts (*i.e.*, C2C12 cells) [38, 40]. Therefore, the expressions of atrogen-1 and IGF-1 are considered to be directly modulated by glucocorticoids and androgens in muscle cells. Because IGF-1 has a common ARE/GRE site [41], AR and GR may competitively regulate the expression of IGF-1 in muscle cells.

Lipid metabolism in and adipose tissue and liver

Lipid metabolism is largely composed of the fatty acid oxidation of triglyceride (lipolysis) to produce energy and the synthesis of triglyceride (lipogenesis) to store as an energy source. The fatty acid synthesis reactions by fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) are the rate-limiting steps for lipogenesis, whereas the hydrolysis reactions of triglyceride by adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are the rate-limiting steps for lipolysis [42]. FAS and ACC are direct targets of SREBP-1c [43]. Glucocorticoids have both short-term and long-term effects on adipose tissue [44]. As a short-term effect, glucocorticoids increase lipolysis through induction of ATGL and HSL [44], whereas as a long-term effect, they increase adipose tissue and lead to central (abdominal) adiposity [44-46]. The long-term effects causing central adiposity are observed in patients with Cushing's syndrome [45] and in patients treated with exogenous corticosteroid treatment [46]. Unlike their anabolic actions in muscle, androgens have catabolic functions in adipose tissue [47-50]. Low testosterone levels are associated with visceral obesity in men [47, 48], and AR knockout (KO) male mice exhibit obesity [49, 50]. Moreover, testosterone treatment reverses the increase of body fat mass induced by glucocorticoids [9]. Because the HSL level is lower in AR-KO mice than in wild-type mice [50], regulation of HSL expression determines the balance of androgen and glucocorticoid functions in adipocytes. However, because adipose tissue-specific AR-KO mice exhibit increased HSL levels in adipose tissue [51], the decrease of HSL in global AR-KO mice [50] may be an indirect result of the deficiency in androgen action in other tissues. DEX promotes differentiation of 3T3-L1 preadipocytes to mature adipocytes [52], suggesting that glucocorticoids have a role in adipogenesis. In contrast, androgens reduce the differentiation of 3T3-L1 cells [53]. However, it is difficult to conclude that this reduction is due to the suppression of glucocorticoid signaling because differentiation of 3T3-L1 is needed for the activations of other types of signaling (*e.g.*, insulin signaling and PKA signaling by isobutylmethylxanthine). Glucocorticoids inactivate DHT by inducing the expression of aldo-keto reductase 1C2, which metabolizes DHT to 5α-androstane-3α, 17β-diol [54], reducing the overall function of DHT in adipocytes. Although androgens and glucocorticoids have at least partially opposing effects on lipolysis in adipocytes and the differentiation of preadipocytes, the mechanism underlying the competition remains largely unknown.

In hepatocytes, DEX decreases the expression of 5α-reductase 1 which converts testosterone to DHT [55]. DEX increases lipogenesis by inducing the expressions of SREBP-1c, FAS, and ACC in the presence of insulin [44, 56, 57]. Castration increases and testosterone treatment decreases the

expressions of SREBP-1c, FAS, and ACC, which regulate hepatic triglyceride levels [58]. Hepatocyte-specific AR-KO also increases SREBP-1c and ACC in liver [59]. Stearoyl-CoA desaturase 1, which is a major target of SREBP-1c, is increased in hepatic AR-KO mice liver, and the increase is observed even in hepatocytes isolated from the KO mice [59]. Taken together, these results suggest that androgens and glucocorticoids exert opposite effects on lipolysis in adipocytes and opposite effects on lipogenesis in hepatocytes by differently regulating the rate-limiting enzymes.

Pancreatic β-cell death

Glucocorticoids induce apoptotic cell death in pancreatic β-cells, T-cell lymphoma cells, and osteoblasts [6, 60, 61]. These processes are considered to contribute to the pro-diabetic, immunosuppressive, and osteoporotic actions of glucocorticoids. Glucocorticoids induce the expressions of thioredoxin-interacting protein (TXNIP) in all these cells [61-63], and the induction of TXNIP is found to be required for glucocorticoid-induced apoptosis [61, 62]. TXNIP binds to thioredoxin, which in turn causes the dissociation of apoptosis signal-regulating kinase 1 (ASK1) from thioredoxin. Thus, an increase of TXNIP results in an activation of ASK1, which triggers apoptosis through activating JNK/p38 signaling [64]. In β-cells, androgens suppress DEX-induced apoptosis by activating AR [31]. Androgen also suppresses TXNIP expression at the mRNA level in the presence of DEX. The AR mutant AR (C619Y), which is unable to bind to DNA [65], fails to suppress DEX-stimulated activation of the TXNIP (-1081/+20) promoter, indicating that the DNA-binding of AR is required for suppression of TXNIP. Moreover, AR and GR share the same ARE/GRE site (-851/-837) on the TXNIP promoter [31, 62], and competitive binding between ligand-bound AR and GR on the TXNIP promoter was confirmed by ChIP assays [31]. AR binding to the TXNIP promoter, which is ligand dependent, doesn't affect the basal expression of TXNIP in the absence of DEX in β-cells. These results illustrate that AR and GR compete for binding to the same ARE/GRE site of the TXNIP promoter as a silencer and enhancer, respectively, and thus negatively and positively regulate β-cell death, respectively. It is postulated that AR/GR heterodimers can interfere with the function of AR and GR homodimers [66]. However, a heterodimer in which AR is ligand-free and GR is ligand-bound does not bind to the TXNIP promoter, and vice versa. It is unclear whether a heterodimer composed of ligand-bound AR and ligand-bound GR can bind to the ARE/GRE site. Therefore, it is unclear whether the heterodimer has a role in regulating TXNIP expression. Because TXNIP also plays an important role in insulin secretion [67], these types of regulation of TXNIP may partly account for glucocorticoid-suppressed [68] and androgen-increased insulin secretion [69].

TXNIP is crucial for diverse cellular processes such as inflammation, ER-stress, glucose homeostasis, obesity, and cancer progression [64, 70-73]. The ARE/GRE site (-851/-837) of the TXNIP promoter is widely conserved among mammals. Microarray analyses suggest that TXNIP is an AR-repressed gene in various cells, such as prostate cells and dermal papilla cells [74, 75]. Therefore, competitive binding between AR and GR on the ARE/GRE of TXNIP promoter may be involved in controlling a variety of cellular functions.

Compensatory effect between androgen and glucocorticoid

Recurrence of prostate cancer

AR is a master regulator of cell proliferation in primary prostate cancer [76]. Androgen deprivation therapy such as surgical or chemical castration (*i.e.*, LH-RH analog and antiandrogen) is a standard therapy for treatment of prostate cancer. However, prostate cancer often recurs as a castration-resistant prostate cancer (CRPC) with poor prognosis [77]. Antiandrogen (ARN-509 or RD162) treatment in mice grafted with human prostate cancer cells resulted in the increases of GR and several AR target genes (*e.g.*, SGK1 and PSA), [30]. Similar results were observed in bone metastases from CRPC patients receiving an antiandrogen (enzalutamide) [30]. The development of CRPC is further enhanced by administration of DEX, whereas a GR antagonist or GR silencing each reduces the proliferation of CRPC cells without affecting AR expression, indicating that GR compensates for the loss of AR function [30]. The increased GR activates a similar, but distinguishable, set of target genes, suggesting that CRPC development is not due to complete compensation by GR [30]. Isikbay *et al.* [78] also demonstrated the importance of glucocorticoid signaling in the development of CRPC using a mouse xenograft model of human CRPC cells. They showed that glucocorticoid-mediated proliferation of CRPC cells was suppressed by not only a GR antagonist but also by the SGK1 inhibitor GSK650394, and that knockdown of GR increased, and overexpression of SGK1 decreased, tumor-free survival in castrated mice [78]. These results suggest that SGK1 is a key protein for the compensation of AR action by GR. This idea is supported by the finding that GR is repressed by AR signaling in hormone-sensitive prostate cancer cells [79]. In CRPC model cells, DHT and DEX upregulated 105 and 121 genes, respectively, 52 of which were upregulated by both steroids [30]. In addition, a ChIP-seq experiment showed that 52% of AR-binding sites are also GR-binding sites [26, 30]. Similarly, approximately

half of AR-binding sites were also found to be bound by GR in another prostate cancer cell line [26]. Taken together, these results show that GR partially compensates for the loss of AR function and steadily leads to the development of CRPC.

Summary

Glucocorticoids, in addition to reducing blood testosterone levels [10], reduce DHT levels by decreasing 5α-reductase 1 in hepatocytes [55] and inactivate DHT by inducing aldo-keto reductase 1C2 in adipocytes [54]. In muscular cells *in vivo*, administration of glucocorticoids reduces AR expression and administration of androgens reduces GR expression [10, 36]. However, it is not clear whether these effects are direct or indirect effects of the steroids. On the other hand, androgen directly suppresses the expression of GR in prostate [30], but not in β-cells [31]. Recent results indicate that target genes are competitively regulated at the same ARE/GRE site [30, 31]. These findings indicate that the interference between AR signaling and GR signaling affects the expressions of target genes by at least three different mechanisms: (i) regulation of applicable ligand levels by modulation of steroid metabolite enzyme levels, (ii) regulation of the receptor levels and (iii) competitive binding between AR and GR on the common ARE/GRE sites. Although the physiological relevance of heterodimerization of AR and GR is not clear, heterodimerization could also modulate AR and GR function [66]. The regulation of genes mediated by the ARE/GRE is considered to be more complicated because the ARE/GRE sequence can be also recognized by mineralocorticoid receptor and progesterone receptor [18].

After androgen-deprivation therapy, GR compensates for the loss of AR function and promotes the proliferation of prostate cancer, leading to the development of CRPC [30]. However, GR signaling represses rather than promotes the proliferation of prostate cells in the presence of androgens [80]. Therefore, the role of GR depends on the level of activity of AR. Previous results, taken together, show that (i) androgen and glucocorticoid principally exert opposite effects in various physiological processes, and that (ii) the ability of one to compensate for loss of the other has been observed only in a pathophysiological process (*viz.*, CRPC) [30]. The regulation of key genes seems to directly govern the overall effects of androgen and glucocorticoid on cell function. Examples of such genes and their cell functions include IGF-1 and atrogin-1 in muscle mass, TXNIP in β-cell death, and SGK1 in CRPC development. When key genes are inversely regulated by AR and GR, androgen and glucocorticoid exert opposite effects.

Conflicts of interest

The authors have no conflict of interest.

Acknowledgements

We thank our funding sources: Grants-in-Aid for scientific research from the Japan Society for the Promotion of Science (25450176, to N.H. and 26560065, to H.I.).

Abbreviations

ACC: acetyl-CoA carboxylase; ATGL: adipose triglyceride lipase; AR: androgen receptor; ARE: androgen-response element; ASK1: apoptosis signal-regulating kinase 1; CRPC: castration-resistant prostate cancer; DEX: dexamethasone; DHT: dihydrotestosterone; DBD: DNA-binding domain; FAS: fatty acid synthase; FOXO1: forkhead box O1; GR: glucocorticoid receptor; GRE: glucocorticoid-response element; HSL: hormone-sensitive lipase; IGF-1: insulin-like growth factor-1; KO: knockout; LBD: ligand-binding domain; NTD: N-terminal domain; PSA: prostate-specific antigen; SGK1: serum/glucocorticoid-regulated kinase 1; TXNIP: thioredoxin-interacting protein.

References

1. Kerkhofs S, Denayer S, Haelens A, Claessens F. Androgen receptor knockout and knock-in mouse models. J Mol Endocrinol 2009; 42: 11-17.
2. Chang C, Yeh S, Lee SO, Chang T-m. Androgen Receptor (AR) Pathophysiological Roles in Androgen Related Diseases in Skin, Bone/Muscle, Metabolic Syndrome and Neuron/Immune Systems: Lessons Learned from Mice Lacking AR in Specific Cells. Nucl Recept Signal 2013; 11: e001.
3. Rana K, Davey RA, Zajac JD. Human androgen deficiency: insights gained from androgen receptor knockout mouse models. Asian J Androl 2014; 16: 169-177.
4. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab 2009; 94 :2692-2701.
5. Ito K, Chung KF, Adcock IM. Update on glucocorticoid action and resistance. J Allergy Clin Immunol 2006; 117: 522-543.
6. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2007; 18: 1319-1328.
7. Braun TP, Marks DL. The regulation of muscle mass by endogenous glucocorticoids. Front Physiol 2015; 6: 12.
8. Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. Int J Biochem Cell Biol 2013; 45: 2163-2172.
9. Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy

in glucocorticoid-treated men. Arch Intern Med 1996; 156: 1173-1177.

10. Inder WJ, Jang C, Obeyesekere VR, Alford FP. Dexamethasone administration inhibits skeletal muscle expression of the androgen receptor and IGF-1--implications for steroid-induced myopathy. Clin Endocrinol 2010; 73: 126-132.
11. Gibson A. The effect of testosterone and of castration on anococcygeus muscle contractility and on plasma corticosterone levels in the rat. Eur J Pharmacol 1977; 41: 7-11.
12. McKenna NJ, O'Malley BW. Combinatorial control of gene expression by nuclear receptors and coregulators. Cell 2002; 108: 465-474.
13. Heinlein CA, Chang C. Androgen receptor (AR) coregulators: an overview. Endocr Rev 2002; 23: 175-200.
14. Wang L, Hsu CL, Chang C. Androgen receptor corepressors: an overview. Prostate 2005; 63: 117-130.
15. Prescott J, Jariwala U, Jia L, Cogan JP, Barski A, Pregizer S, *et al*. Androgen receptor-mediated repression of novel target genes. Prostate 2007; 67: 1371-1383.
16. Perissi V, Aggarwal A, Glass CK, Rose DW, Rosenfeld MG. A corepressor/coactivator exchange complex required for transcriptional activation by nuclear receptors and other regulated transcription factors. Cell 2004; 116: 511-526.
17. Hodgson MC, Shen HC, Hollenberg AN, Balk SP. Structural basis for nuclear receptor corepressor recruitment by antagonist-liganded androgen receptor. Mol Cancer Ther 2008; 7: 3187-3194.
18. Evans RM. The steroid and thyroid hormone receptor superfamily. Science 1988; 240: 889-895.
19. Shaffer PL, Jivan A, Dollins DE, Claessens F, Gewirth DT. Structural basis of androgen receptor binding to selective androgen response elements. Proc Natl Acad Sci U S A 2004; 101: 4758-4763.
20. Claessens F, Verrijdt G, Schoenmakers E, Haelens A, Peeters B, Verhoeven G, *et al*. Selective DNA binding by the androgen receptor as a mechanism for hormone-specific gene regulation. J Steroid Biochem Mol Biol 2001; 76: 23-30.
21. Claessens F, Denayer S, Van Tilborgh N, Kerkhofs S, Helsen C, Haelens A. Diverse roles of androgen receptor (AR) domains in AR-mediated signaling. Nucl Recept Signal 2008; 6: e008.
22. Margolis RN, Evans RM, O'Malley BW. The Nuclear Receptor Signaling Atlas: development of a functional atlas of nuclear receptors. Mol Endocrinol 2005; 19: 2433-2436.
23. Harada N, Takagi T, Nakano Y, Yamaji R, Inui H. Protein arginine methyltransferase 10 is required for androgen-dependent proliferation of LNCaP prostate cancer cells. Biosci Biotechnol Biochem 2015; DOI: 10.1080/09168451.2015.1025035.
24. Massie CE, Adryan B, Barbosa Morais NL, Lynch AG, Tran MG, Neal DE, *et al*. New androgen receptor genomic targets show an interaction with the ETS1 transcription factor. EMBO Rep 2007; 8: 871-878.
25. Wang Q, Li W, Liu XS, Carroll JS, Janne OA, Keeton EK, *et al*. A hierarchical network of transcription factors governs androgen receptor-dependent prostate cancer growth. Mol Cell 2007; 27: 380-392.
26. Sahu B, Laakso M, Pihlajamaa P, Ovaska K, Sinielnikov I, Hautaniemi S, *et al*. FoxA1 specifies unique androgen and glucocorticoid receptor binding events in prostate cancer cells. Cancer Res 2013; 73: 1570-1580.
27. John S, Sabo PJ, Thurman RE, Sung MH, Biddie SC, Johnson TA, *et al*. Chromatin accessibility pre-determines glucocorticoid receptor binding patterns. Nat Genet 2011; 43: 264-268.
28. Cleutjens CB, Steketee K, van Eekelen CC, van der Korput JA, Brinkmann AO, Trapman J. Both androgen receptor and glucocorticoid receptor are able to induce prostate-specific antigen expression, but differ in their growth-stimulating properties of LNCaP cells. Endocrinology 1997; 138: 5293-5300.
29. Sherk AB, Frigo DE, Schnackenberg CG, Bray JD, Laping NJ, Trizna W, *et al*. Development of a small-molecule serum- and glucocorticoid-regulated kinase-1 antagonist and its evaluation as a prostate cancer therapeutic. Cancer Res 2008; 68: 7475-7483.
30. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, *et al*. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 2013; 155: 1309-1322.
31. Harada N, Katsuki T, Takahashi Y, Masuda T, Yoshinaga M, Adachi T, *et al*. Androgen receptor silences thioredoxin-interacting protein and competitively inhibits glucocorticoid receptor-mediated apoptosis in pancreatic β-cells. J Cell Biohem 2015; 116: 998-1006.
32. Fanzani A, Conraads VM, Penna F, Martinet W. Molecular and cellular mechanisms of skeletal muscle atrophy: an update. J Cachexia Sarcopenia Muscle 2012; 3: 163-179.
33. Egerman MA, Glass DJ. Signaling pathways controlling skeletal muscle mass. Crit Rev Biochem Mol Biol 2014; 49: 59-68.
34. Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. Int J Biochem Cell Biol 2005; 37: 1974-1984.
35. Borst SE. Interventions for sarcopenia and muscle weakness in older people. Age Ageing 2004; 33: 548-555.
36. Ye F, McCoy SC, Ross HH, Bernardo JA, Beharry AW, Senf SM, *et al*. Transcriptional regulation of myotrophic actions by testosterone and trenbolone on androgen-responsive muscle. Steroids 2014; 87: 59-66.
37. Qin W, Pan J, Wu Y, Bauman WA, Cardozo C. Protection against dexamethasone-induced muscle atrophy is related to modulation by testosterone of FOXO1 and PGC-1alpha. Biochem Biophys Res Commun 2010; 403: 473-478.
38. Jones A, Hwang DJ, Narayanan R, Miller DD, Dalton JT. Effects of a novel selective androgen receptor modulator on dexamethasone-induced and hypogonadism-induced muscle atrophy. Endocrinology 2010; 151: 3706-3719.
39. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. J Clin Endocrinol Metab 2003; 88: 3167-3176.
40. Zhao W, Pan J, Zhao Z, Wu Y, Bauman WA, Cardozo CP. Testosterone protects against dexamethasone-induced muscle atrophy, protein degradation and MAFbx upregulation. J Steroid Biochem Mol Biol 2008; 110: 125-129.
41. Wu Y, Zhao W, Zhao J, Pan J, Wu Q, Zhang Y, *et al.*

Identification of androgen response elements in the insulin-like growth factor I upstream promoter. Endocrinology 2007; 148: 2984-2993.

42. Duncan RE, Ahmadian M, Jaworski K, Sarkadi-Nagy E, Sul HS. Regulation of lipolysis in adipocytes. Annu Rev Nutr 2007; 27: 79-101.

43. Shimano H. Sterol regulatory element-binding protein-1 as a dominant transcription factor for gene regulation of lipogenic enzymes in the liver. Trends Cardiovasc Med 2000; 10: 275-278.

44. Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism 2011; 60: 1500-1510.

45. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, *et al*. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008; 93: 1526-1540.

46. Dallman MF, la Fleur SE, Pecoraro NC, Gomez F, Houshyar H, Akana SF. Minireview: glucocorticoids--food intake, abdominal obesity, and wealthy nations in 2004. Endocrinology 2004; 145: 2633-2638.

47. Blouin K, Boivin A, Tchernof A. Androgens and body fat distribution. J Steroid Biochem Mol Biol 2008; 108: 272-280.

48. De Maddalena C, Vodo S, Petroni A, Aloisi AM. Impact of testosterone on body fat composition. J Cell Physiol 2012; 227: 3744-3748.

49. Sato T, Matsumoto T, Yamada T, Watanabe T, Kawano H, Kato S. Late onset of obesity in male androgen receptor-deficient (AR KO) mice. Biochem Biophys Res Commun 2003; 300: 167-171.

50. Fan W, Yanase T, Nomura M, Okabe T, Goto K, Sato T, *et al*. Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion. Diabetes 2005; 54: 1000-1008.

51. McInnes KJ, Smith LB, Hunger NI, Saunders PT, Andrew R, Walker BR. Deletion of the androgen receptor in adipose tissue in male mice elevates retinol binding protein 4 and reveals independent effects on visceral fat mass and on glucose homeostasis. Diabetes 2012; 61: 1072-1081.

52. Wu Z, Bucher NL, Farmer SR. Induction of peroxisome proliferator-activated receptor gamma during the conversion of 3T3 fibroblasts into adipocytes is mediated by C/EBPbeta, C/EBPdelta, and glucocorticoids. Mol Cell Biol 1996; 16: 4128-4136.

53. Singh R, Artaza JN, Taylor WE, Braga M, Yuan X, Gonzalez Cadavid NF, *et al*. Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. Endocrinology 2006; 147: 141-154.

54. Veilleux A, Cote JA, Blouin K, Nadeau M, Pelletier M, Marceau P, *et al*. Glucocorticoid-induced androgen inactivation by aldo-keto reductase 1C2 promotes adipogenesis in human preadipocytes. Am J Physiol Endocrinol Metab 2012; 302: E941-949.

55. El-Awady MK, El-Garf W, El-Houssieny L. Steroid 5alpha reductase mRNA type 1 is differentially regulated by androgens and glucocorticoids in the rat liver. Endocr J 2004; 51: 37-46.

56. Prip-Buus C, Perdereau D, Foufelle F, Maury J, Ferre P, Girard J. Induction of fatty-acid-synthase gene expression by glucose in primary culture of rat hepatocytes. Dependency upon glucokinase activity. Eur J Biochem 1995; 230: 309-315.

57. Ma WL, Lai HC, Yeh S, Cai X, Chang C. Androgen receptor roles in hepatocellular carcinoma, fatty liver, cirrhosis and hepatitis. Endocr Relat Cancer 2014; 21: R165-182.

58. Senmaru T, Fukui M, Okada H, Mineoka Y, Yamazaki M, Tsujikawa M, *et al*. Testosterone deficiency induces markedly decreased serum triglycerides, increased small dense LDL, and hepatic steatosis mediated by dysregulation of lipid assembly and secretion in mice fed a high-fat diet. Metabolism 2013; 62: 851-860.

59. Lin HY, Yu IC, Wang RS, Chen YT, Liu NC, Altuwaijri S, *et al*. Increased hepatic steatosis and insulin resistance in mice lacking hepatic androgen receptor. Hepatology 2008; 47: 1924-1935.

60. Ranta F, Avram D, Berchtold S, Dufer M, Drews G, Lang F, *et al*. Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4. Diabetes 2006; 55: 1380-1390.

61. Wang Z, Rong YP, Malone MH, Davis MC, Zhong F, Distelhorst CW. Thioredoxin-interacting protein (txnip) is a glucocorticoid-regulated primary response gene involved in mediating glucocorticoid-induced apoptosis. Oncogene 2006; 25: 1903-1913.

62. Reich E, Tamary A, Sionov RV, Melloul D. Involvement of thioredoxin-interacting protein (TXNIP) in glucocorticoid-mediated beta cell death. Diabetologia 2012; 55: 1048-1057.

63. Lekva T, Ueland T, Boyum H, Evang JA, Godang K, Bollerslev J. TXNIP is highly regulated in bone biopsies from patients with endogenous Cushing's syndrome and related to bone turnover. Eur J Endocrinol 2012; 166: 1039-1048.

64. Yoshihara E, Masaki S, Matsuo Y, Chen Z, Tian H, Yodoi J. Thioredoxin/Txnip: redoxisome, as a redox switch for the pathogenesis of diseases. Front Immunol 2014, 4: 514.

65. Nazareth LV, Stenoien DL, Bingman WE 3rd, James AJ, Wu C, Zhang Y, *et al*. A C619Y mutation in the human androgen receptor causes inactivation and mislocalization of the receptor with concomitant sequestration of SRC-1 (steroid receptor coactivator 1). Mol Endocrinol 1999; 13: 2065-2075.

66. Chen S, Wang J, Yu G, Liu W, Pearce D. Androgen and glucocorticoid receptor heterodimer formation. A possible mechanism for mutual inhibition of transcriptional activity. J Biol Chem 1997; 272: 14087-14092.

67. Oka S, Yoshihara E, Bizen-Abe A, Liu W, Watanabe M, Yodoi J, *et al*. Thioredoxin binding protein-2/thioredoxin-interacting protein is a critical regulator of insulin secretion and peroxisome proliferator-activated receptor function. Endocrinology 2009; 150: 1225-1234.

68. Lambillotte C, Gilon P, Henquin JC. Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. J Clin Invest 1997; 99: 414-423.

69. Morimoto S, Fernandez-Mejia C, Romero-Navarro G, Morales-Peza N, Diaz-Sanchez V. Testosterone effect on insulin content, messenger ribonucleic acid levels, promoter activity, and secretion in the rat. Endocrinology 2001; 142: 1442-1447.

70. Chen J, Hui ST, Couto FM, Mungrue IN, Davis DB, Attie AD, *et*

al. Thioredoxin-interacting protein deficiency induces Akt/Bcl-xL signaling and pancreatic beta-cell mass and protects against diabetes. FASEB J 2008; 22: 3581-3594.

71. Oslowski CM, Hara T, O'Sullivan-Murphy B, Kanekura K, Lu S, Hara M, *et al*. Thioredoxin-interacting protein mediates ER stress-induced beta cell death through initiation of the inflammasome. Cell Metab 2012; 16: 265-273.
72. Chutkow WA, Birkenfeld AL, Brown JD, Lee HY, Frederick DW, Yoshioka J, *et al*. Deletion of the alpha-arrestin protein Txnip in mice promotes adiposity and adipogenesis while preserving insulin sensitivity. Diabetes 2010; 59: 1424-1434.
73. Zhou J, Chng WJ. Roles of thioredoxin binding protein (TXNIP) in oxidative stress, apoptosis and cancer. Mitochondrion 2013; 13: 163-169.
74. Velasco AM, Gillis KA, Li Y, Brown EL, Sadler TM, Achilleos M, *et al*. Identification and validation of novel androgen-regulated genes in prostate cancer. Endocrinology 2004; 145: 3913-3924.
75. Park SY, Kwack MH, Chung EJ, Im SU, Han IS, Kim MK, *et al*. Establishment of SV40T-transformed human dermal papilla cells and identification of dihydrotestosterone-regulated genes by cDNA microarray. J Dermatol Sci 2007; 47: 201-208.
76. Heinlein CA, Chang C. Androgen receptor in prostate cancer. Endocr Rev 2004; 25: 276-308.
77. Chen Y, Sawyers CL, Scher HI. Targeting the androgen receptor pathway in prostate cancer. Curr Opin Pharmacol 2008; 8: 440-448.
78. Isikbay M, Otto K, Kregel S, Kach J, Cai Y, Vander Griend DJ, *et al*. Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. Horm Cancer 2014; 5: 72-89.
79. Xie N, Cheng H, Lin D, Liu L, Yang O, Jia L, *et al*. The expression of glucocorticoid receptor is negatively regulated by active androgen receptor signaling in prostate tumors. Int J Cancer 2015; 136: E27-38.
80. Yemelyanov A, Czwornog J, Chebotaev D, Karseladze A, Kulevitch E, Yang X, *et al*. Tumor suppressor activity of glucocorticoid receptor in the prostate. Oncogene 2007; 26: 1885-1896.