Journal of Steroid Biochemistry & Molecular Biology 119 (2010) 56–72

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

11β-Hydroxysteroid dehydrogenase type 1 is an important regulator at the interface of obesity and inflammation

Claudia A. Staab, Edmund Maser*

Institute of Toxicology and Pharmacology for Natural Scientists, University Medical School Schleswig-Holstein, Campus Kiel, Brunswiker Str. 10, 24105 Kiel, Germany

ARTICLE INFO

Article history:
Received 23 October 2009
Received in revised form
17 December 2009
Accepted 21 December 2009

Keywords:
11β-HSD1
Obesity
Metabolic syndrome
Syndrome X
Insulin resistance
Glucocorticoid response

ABSTRACT

Systemic glucocorticoid excess, as exemplified by the Cushing syndrome, leads to obesity and all further symptoms of the metabolic syndrome. The current obesity epidemic, however, is not characterized by increased plasma cortisol concentrations, but instead comes along with chronic low-grade inflammation in adipose tissue and concomitant increased levels of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1, gene *HSD11B1*), a parameter known to cause obesity in a mouse model. 11β-HSD1 represents an intracellular amplifier of active glucocorticoid, thus enhances the associated effects on the inflammatory response as well as on nutrient and energy metabolism, and may therefore cause and exacerbate obesity by local increase of glucocorticoid concentrations. Obtained by extensive literature and database searching, the present review includes comprehensive lists of primary glucocorticoid-sensitive genes and gene products as well as of the thus far known regulators of *HSD11B1* expression with implication in inflammation and metabolic disease. Collectively, the data clearly show that, in addition to amplifying active glucocorticoid and thus profoundly modulating inflammation and nutrient metabolism, 11β-HSD1 is subject to tight control of multiple additional immunomodulatory and metabolic regulators. Hence, 11β-HSD1 acts at the interface of inflammation and obesity and represents an efficient integrator and effector of local inflammatory and metabolic state.

1. Introduction

The striking resemblances between symptoms of hypercortisolism (also known as Cushing syndrome) and symptoms of the metabolic syndrome have initiated intensive investigations on the potential aetiological role of glucocorticoids in the current obesity epidemic. Glucocorticoids (cortisol and cortisone in man, corticosterone and dehydrocorticosterone in rodents) are synthesized in and secreted from the *zona fasciculata* of the adrenal gland, under control of adrenocorticotropic hormone (ACTH, also known as corticotropin) which is secreted from the anterior pituitary gland. The secretion of ACTH in turn is regulated by vasopressin and corticotropin-releasing hormone (CRH), both peptide hormones that originate in the hypothalamus. This complex set of hormone interactions and regulations is often referred to as the hypothalamus–pituitary–adrenal (HPA) axis.

Serum glucocorticoids readily pass cell membranes and exert their intracellular functions by binding to the glucocorticoid receptor (GR), a ligand-activated nuclear receptor which regulates the expression of a plethora of genes involved in various physiological processes including energy metabolism and inflammation. However, this receptor only binds the reduced form, *e.g.* cortisol, with high affinity. Two microsomal enzymes collectively referred to as the 11β-hydroxysteroid dehydrogenase (11β-HSD) system interconvert receptor-active cortisol and inert cortisone and, through intracellular cortisol amplification or inactivation, represent an additional regulatory step prior to glucocorticoid action (Fig. 1).

Hence, glucocorticoid functions are subject to several levels of regulation, and an exaggerated glucocorticoid response – as observed in the metabolic syndrome – might be a result of excess glucocorticoid secretion by the HPA axis, increased intracellular GR density or deregulated intracellular glucocorticoid prereceptor metabolism by the 11β-HSD system. During the last 10 years, evidence has accumulated that strongly argues for an aetiological role of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in obesity and the metabolic syndrome [1–7]. At the same time, increasingly more studies support a function for 11β-HSD1 in inflammation [8–15]. Interestingly, adiposity has

Abbreviations: ACTH, adrenocorticotropic hormone; AP-1, activator protein-1; C/EBP, CCAAT-enhancer-binding protein; CRH, corticotropin-releasing hormone; GH, growth hormone; GR, glucocorticoid receptor; GREs, glucocorticoid-response elements; 11β-HSD, 11β-hydroxysteroid dehydrogenase; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; HPA, hypothalamus–pituitary–adrenal; IFN-γ, interferon γ; IGF-I, insulin-like growth factor-I; IL, interleukin; IRS1, insulin receptor substrate 1; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; PKA, protein kinase A; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.

* Corresponding author. Tel.: +49 431 597 3540; fax: +49 431 597 3558.
E-mail address: maser@toxi.uni-kiel.de (E. Maser).

0960-0760/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2009.12.013

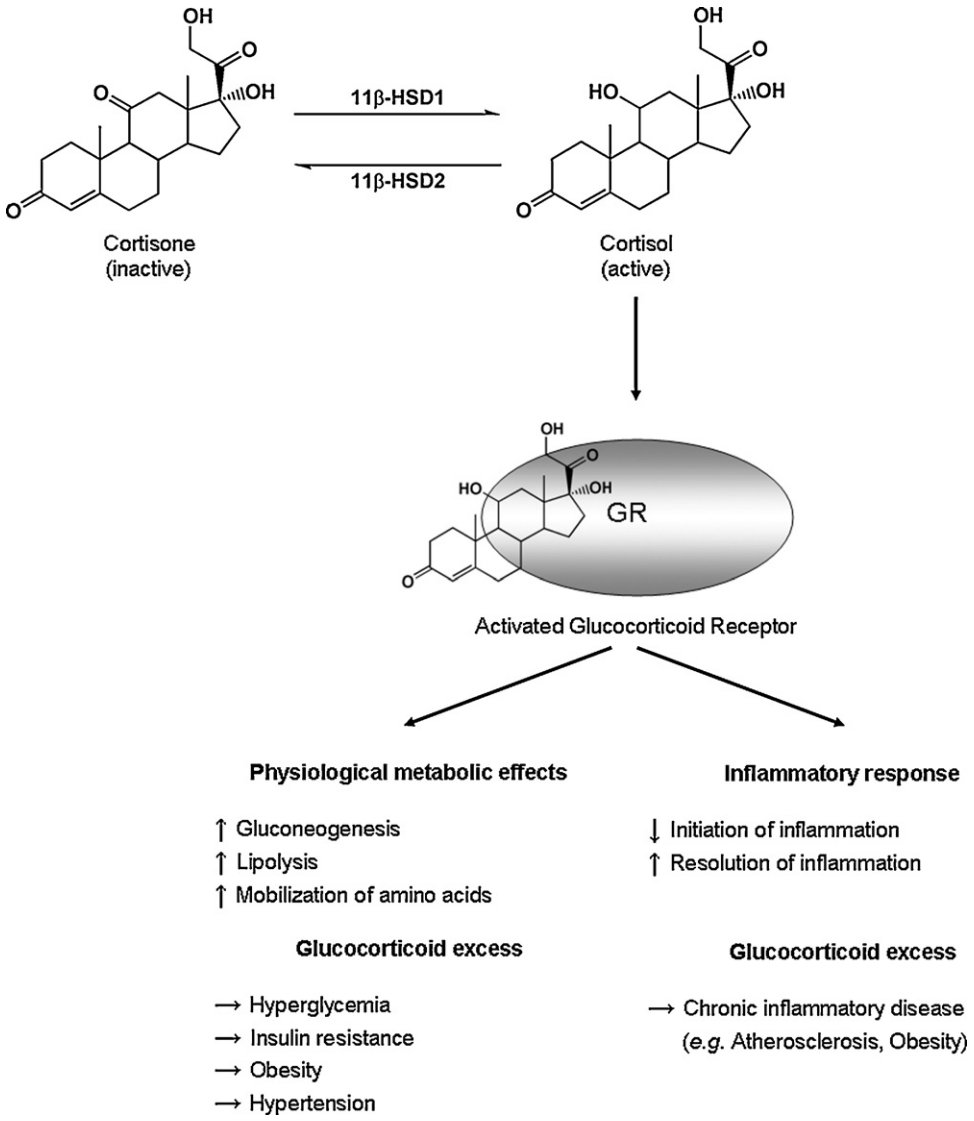

Fig. 1. Interconversion of cortisone and cortisol by the 11β-HSD system and glucocorticoid responses. 11β-HSD1 reduces receptor-inactive cortisone to cortisol which can bind to the glucocorticoid receptor (GR). The hereby activated GR modulates expression of numerous genes involved in nutrient metabolism as well as inflammation. Physiological effects in terms of metabolism include the stimulation of lipolysis in adipose tissue, of protein degradation and amino acid mobilization from muscle, and of hepatic gluconeogenesis. During the normal inflammatory response, glucocorticoids suppress the initiation and promote the resolution of inflammation. In contrast, glucocorticoid excess can cause all symptoms of the metabolic syndrome including hyperglycaemia, insulin resistance, obesity and hypertension, as well as contribute to chronic inflammatory diseases.

been shown to associate with an increase of macrophage numbers and pro-inflammatory cytokines in adipose tissue [16–19]. Hence, 11β-HSD1 might function as an important regulator at the interface of inflammation and obesity.

Within this review, we will present support for this hypothesis in form of a comprehensive list of GR-regulated genes with implication in metabolic/inflammatory disease and a summary of the thus far published transcription factors/agonists with known implication in energy metabolism and inflammation that modulate intracellular 11β-HSD1 activity.

2. Glucocorticoids and glucocorticoid receptor in metabolic and inflammatory disease

2.1. Glucocorticoids and glucocorticoid receptor in the aetiology of the metabolic syndrome

Glucocorticoid treatment of inflammatory diseases or excess secretion of cortisol by the adrenal cortex results in the Cushing syndrome, with symptoms closely reflecting the metabolic syndrome, *i.e.* obesity, insulin resistance, hypertension and an unfavourable lipid and lipoprotein profile [20]. Furthermore, monogenic rodent models for the metabolic syndrome, *e.g.* the leptin-deficient ob/ob mouse or the leptin-resistant Zucker rat, display overall increased secretion of glucocorticoids [21,22]. These observations have driven researchers to investigate whether increased adrenal cortisol secretion is a direct cause of the current global obesity epidemic. However, obese patients exhibit mostly unchanged or sometimes even decreased systemic cortisol levels [2]. Hence, common obesity, as usually caused by excess calorie intake and lack of physical activity, does not come along with an HPA-dependent increase in systemic glucocorticoid levels as Cushing syndrome suggests.

Still, invariant blood glucocorticoid concentrations do not rule out an aetiological role for glucocorticoid excess in the metabolic syndrome. Other mechanisms than excess glucocorticoid secretion can trigger an exaggerated glucocorticoid response and might provide an explanation for the striking similarity between symptoms

of the metabolic syndrome and the Cushing syndrome. Glucocorticoids exert their intracellular effects via the glucocorticoid receptor (gene name *NR3C1*), a ubiquitous ligand-activated nuclear receptor. There exist two alternative splice variants of the GR, termed GRα and GRβ [23,24]. Whereas GRα is the classic GR, *i.e.* mediates glucocorticoid effects, GRβ does not bind glucocorticoids and thus far its functions are a subject of controversy [25,26]. There is evidence that GRβ may act as a dominant negative inhibitor of GRα, apparently by the formation of GRα/GRβ heterodimers which prevent GRα homodimerization [27,28]. Additionally, specific targets for GRβ-mediated transcriptional activity, independent of glucocorticoids and GRα, have been identified recently [24,29]. Hence, not mere *NR3C1* overexpression but also dysregulation of the intracellular GRα/GRβ ratio could underlie altered tissue sensitivity to glucocorticoids in the metabolic syndrome, but this subject has not received much attention so far [30].

In absence of its cognate ligand cortisol, the GRα is retained in the cytoplasm in form of a heteromultimeric complex with chaperones and immunophilins, as *e.g.* the heat shock proteins HSP70 and HSP90 and FK506-binding proteins FKBP51 and FKBP52 [31,32]. Binding of cortisol leads to the dissociation of the complex and ultimately allows translocation into the nucleus, where the GR homodimer mediates its effects, inducing or repressing target gene transcription (cf. Table 1). Studies with rodent models have shown that selective downregulation of *Nr3c1* expression in liver and adipose tissue by antisense oligonucleotides reduced hyperglycaemia and hyperlipidemia [33]. Hence, *NR3C1* polymorphisms or altered intracellular GR density could contribute to the pathogenesis of obesity and its associated medical complications. But despite the discovery of several interesting *NR3C1* gene polymorphisms their functional implication in the aetiology of the metabolic syndrome is still unclear as appropriate studies have generated conflicting results [34–36]. As to intracellular GR density, studies indicate that GR levels are unchanged or decreased in adipose tissue of obese individuals, thus in part even contrary to anticipated results [30,37]. However, for human skeletal muscle limited findings suggest a positive correlation between insulin resistance, body mass index and *NR3C1* expression [38].

2.2. Glucocorticoids and glucocorticoid receptor in inflammation

Glucocorticoids are potent immunosuppressors and as such routinely used in the treatment of chronic inflammatory disease. In physiological concentrations, they exhibit various anti-inflammatory effects and, overall, suppress initial events of the inflammatory process and promote the resolution of the inflammation at a later stage. In response to inflammation, the HPA axis is activated by the increase in circulating pro-inflammatory cytokines like tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and the adipokine leptin [39,40]. HPA activation then leads to an increased production of serum glucocorticoids which, by virtue of their anti-inflammatory properties, denotes a negative feedback loop for the inflammatory response. Hence, it is not surprising that a deregulation of HPA axis activation contributes to chronic inflammatory disease in several animal disease models [41]. Whether such a deregulation is an aetiological factor in human disease is plausible, but less well established [41–44].

Although deregulated *NR3C1* expression has the potential to contribute to chronic inflammatory disease, only few corresponding studies support this concept, *e.g.* in the context of rheumatoid arthritis [45–47]. Studies on patients suffering from inflammatory bowel disease have provided inconsistent results [48,49]. Hence, similar to observations regarding the metabolic syndrome, altered expression of *NR3C1* appears to be a less important factor in the aetiology of inflammatory disorders.

3. The contribution of 11β-HSD1 to glucocorticoid response

3.1. The 11β-HSD system in glucocorticoid metabolism

The intracellular bioavailability of active glucocorticoids is modulated by the microsomal 11β-hydroxysteroid dehydrogenases which interconvert cortisol and cortisone in man, and corticosterone and 11-dehydrocorticosterone in rodents (Fig. 1) [50–52]. 11β-hydroxysteroid dehydrogenase type 1 mainly acts as an NADPH-dependent reductase, due to its colocalization with hexose-6-phosphate dehydrogenase in the endoplasmic reticulum [53,54]. In contrast, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is an NAD^+-dependent dehydrogenase which inactivates cortisol and corticosterone in man and mice, respectively [55]. As a result, the 11β-HSD1-dependent reaction generates active glucocorticoids which bind to the GR in glucocorticoid target tissues like liver, lung and adipose tissue, while the 11β-HSD2-dependent reaction impedes binding of glucocorticoids to the non-selective mineralocorticoid receptor in mineralocorticoid target tissues as kidney and colon. Hence, glucocorticoid response depends not merely on systemic glucocorticoid levels and intracellular GR activity, but also on intracellular amplification or elimination of bioactive glucocorticoids by 11β-hydroxysteroid dehydrogenases.

The importance of 11β-HSD1 becomes apparent when considering concentrations of free cortisol relative to free cortisone in the blood. Both plasma cortisone and cortisol levels follow a pronounced circadian rhythm and vary from 5 to 100 nM and from 20 to 400 nM, respectively, with a peak in the morning and a nadir at night [56]. (11β-HSD1 expression itself is not subject to circadian rhythm [57].) However, as 85–95% of total plasma cortisol is bound to plasma proteins, particularly to cortisol-binding protein which does not bind cortisone, free plasma cortisone levels mostly exceed free plasma cortisol levels [58,59]. Hence, following diffusion of cortisone across the cell membrane, 11β-HSD1-mediated cortisone reduction can provide GR-activating cortisol against an unfavourable plasma free cortisol/cortisone ratio. Interestingly, 11β-HSD1 exhibits cooperative kinetics with cortisone, but not with cortisol, in a concentration range of 0.1 nM to 75 μM, suggesting that the enzyme is able to dynamically adapt its activity to fluctuating cortisone levels [51].

It should be noted, as an aside, that 11β-HSD1 belongs to the superfamily of short-chain dehydrogenases/reductases (SDR) for which recently a new gene nomenclature has been proposed [60]. According to that nomenclature, the gene encoding human 11β-HSD1 is termed *SDR26C1* and the one encoding human 11β-HSD2 *SDR9C3* [60]. But as this nomenclature currently does not go beyond human SDR enzymes and is not implemented in all common protein databases yet (*e.g.* UniProtKB), we will continue to use the conventional gene nomenclature in this review, *i.e. HSD11B1* and *HSD11B2* for human 11β-HSD1 and 11β-HSD2, respectively, and *Hsd11b1* and *Hsd11b2* for murine 11β-HSD1 and 11β-HSD2.

3.2. 11β-HSD1 in the aetiology of the metabolic syndrome

In contrast to little support for an aetiological role of the GR, compelling evidence has accumulated that argues for 11β-HSD1 as a major aetiological factor in obesity [2–5]. Studies with transgenic rodents as well as clinical studies involving lean and obese humans lend strong support to this concept: 11β-HSD1$^{-/-}$ mice are protected from hyperglycaemia, display an improved cardioprotective serum lipid profile and enhanced hepatic insulin sensitivity [61–63]. Disruption of *Hsd11b1* in an obesity/diabetes-prone strain results in a more favourable adipose tissue distribution as well as protection from diabetes and weight gain upon high-fat feeding [63]. Moreover, modest (about two-fold) upregulation of

Table 1
Primary glucocorticoid receptor (GR, gene *NR3C1*) target genes with implications in metabolic disease and/or inflammation. Direct GR-responsive genes were initially compiled using the "Build/Grow Pathway"-tool in Ingenuity Pathway Analysis (www.ingenuity.com), choosing metabolic disease and "inflammatory response/disease" from "Diseases". Data were then complemented with additional relevant data from the literature. They include interactions identified in human, mouse and rat.

GR target gene	Protein name	Type of interaction	Implications in metabolism, metabolic disease and/or inflammation	References (for the interaction)
AGT	Angiotensinogen	Transcriptional repression	*Metabolic syndrome* (*regulation of blood pressure*) Angiotensin-2 precursor (potent pressor substance)	[139]
AKAP12	A-kinase anchor protein 12	Transcriptional activation	*Inflammatory response* Strongly induced by lipopolysaccharide and the pro-inflammatory cytokine tumor necrosis factor (TNF)-α [140]	[95]
ALOX5AP	Arachidonate 5-lipoxygenase-activating protein	Transcriptional activation	*Inflammatory response* Activator of 5-lipoxygenase-mediated biosynthesis of leukotrienes (inflammatory mediators/chemotactic factors)	[93]
ANGPTL4	Angiopoietin-related protein 4	Transcriptional activation	*Metabolism* Regulator of glucose homeostasis, lipid metabolism, and insulin sensitivity	[93]
B3GNT5	UDP-GlcNAc:βGal β-1,3-N-acetylglucosaminyl-transferase 5	Transcriptional activation	*Metabolism* Glycosphingolipid synthesis	[93]
CCL2	C-C motif chemokine 2	Transcriptional repression	*Inflammatory response* Chemotactic factor, which regulates macrophage recruitment to sites of inflammation [141,142] including adipose tissue [143]	[93]
CCL20	C-C motif chemokine 20	Transcriptional activation	*Inflammatory response* Chemotactic factor that attracts lymphocytes and neutrophils, but not monocytes	[93]
CPS1	Mitochondrial carbamoylphosphate synthetase	Transcriptional activation	*Metabolism* Urea cycle: plays an important role in removing excess ammonia from the cell	[144]
CRH	Corticotropin-releasing hormone	Transcriptional repression	*Feedback regulation* Corticotropin-releasing hormone regulates the release of ACTH from the pituitary gland which results in the synthesis and secretion of glucocorticoids	[145,146]
CYP27A1	Cytochrome P450 27A1	Transcriptional activation	*Metabolism* Metabolism of steroid and vitamin D3 intermediates	[147]
CYP2C9	Cytochrome P450 2C9	Transcriptional activation	*Metabolism* Metabolism of steroids, fatty acids, and xenobiotics	[148]
DNER	Delta/Notch-like epidermal growth factor-related receptor	Transcriptional activation	*Inflammatory response* Activator of the NOTCH1 pathway which regulates expression of genes involved in pro-inflammatory responses, through activation of NF-κB	[88]
DUSP1	Dual specificity protein phosphatase 1	Transcriptional activation	*Inflammatory response* Phosphatase which dephosphorylates and inactivates mitogen-activated protein kinases (MAPKs), notably including p38 MAPK, an important positive regulator of inflammatory gene expression	[87]
EKI2	Ethanolamine kinase 2	Transcriptional activation	*Metabolism* Phospholipid biosynthesis	[93]
FKBP51	FK506-binding protein 5	Transcriptional activation	*Feedback regulation* Part of a heteromultimeric cytoplasmic complex with HSP90, HSP70 and GR; dissociates from the complex when GR binds glucocorticoid	[88,149]

Table 1 (*Continued*)

GR target gene	Protein name	Type of interaction	Implications in metabolism, metabolic disease and/or inflammation	References (for the interaction)
FOXO1	Forkhead box protein O1	Transcriptional activation	*Metabolism* Insulin-induced transcription factor	[88]
GCN2	eIF2α kinase	Transcriptional activation	*Inflammatory response* Phosphorylates eIF2α which leads to induction of NF-κB transcriptional activity [150]	[95]
GHRHR	Growth hormone-releasing hormone receptor	Transcriptional activation	*Metabolism* Increases growth hormone gene transcription and secretion which stimulates the liver and other tissues to secrete insulin-like growth factor-IA	[151]
GLCCI1	Glucocorticoid-induced transcript 1 protein	Transcriptional activation	*Metabolism* Function is unknown, but *GLCCI1*-SNPs associate with diabetes mellitus type 2	[152]
GPR65	Psychosine receptor	Transcriptional activation	*Inflammatory response* Receptor for psychosine, a glycosphingolipid, which may activate the expression of inflammatory cytokines [153]	[95]
HSD11B1	11β-Hydroxysteroid dehydrogenase type 1	Transcriptional activation	*Metabolism* Catalyzes the conversion of inert cortisone to GR-binding cortisol, thus amplifying glucocorticoid action	[131,134]
HSD11B2	11β-Hydroxysteroid dehydrogenase type 2	Transcriptional activation	*Metabolism* Catalyzes the conversion of cortisol to the inactive metabolite cortisone in mineralocorticoid target tissues, thus protecting the non-selective mineralocorticoid receptor from occupation by glucocorticoids	[154]
HTR1A	5-hydroxytryptamine receptor 1A	Transcriptional repression	*Inflammatory response/metabolic syndrome* (*regulation of blood pressure*) Receptor for 5-hydroxytryptamine (serotonin), a mediator of the early inflammatory response and regulator of vascular tone	[155]
IFNB1	Interferon β	Transcriptional activation	*Inflammatory response* Part of the innate immune response, has antiviral, antibacterial and anticancer activities	[156]
IGF1	Insulin-like growth factor-I	Transcriptional activation	*Metabolism* Growth factor, in structure and function related to insulin	[157]
IGFBP1	Insulin-like growth factor-binding protein 1	Transcriptional activation	*Metabolism* Prolongs the half-life of IGFs and thus modulates the growth promoting effects of IGFs	[88,158,159]
IL6	Interleukin 6	Transcriptional repression	*Inflammatory response* Inflammatory cytokine	[160–162]
IL7R	Interleukin-7 receptor subunit α	Transcriptional activation	*Inflammatory response* Receptor for interleukin-7, an inflammatory cytokine	[163]
IL8	Interleukin 8	Transcriptional repression	*Inflammatory response* Inflammatory cytokine	[164,165]
IL11	Interleukin11	Transcriptional repression	*Inflammatory response* Inflammatory cytokine	[93]
INSR	Insulin receptor	Transcriptional activation	*Metabolism* Receptor that mediates the metabolic functions of insulin	[166]
IP6K3	Inositol hexakisphosphate kinase 3	Transcriptional activation	*Metabolism* Involved in the metabolism of inositol phosphates which may act as messengers of cellular energy status [167]	[88]
IRS1	Insulin receptor substrate 1	Transcriptional repression	*Metabolism* Key player in the insulin signalling pathway	[168]

Table 1 (*Continued*)

GR target gene	Protein name	Type of interaction	Implications in metabolism, metabolic disease and/or inflammation	References (for the interaction)
JUN	Proto-oncogene c-jun, forms the heterodimeric transcription factor AP-1 with a member of the Fos family	Inhibition by direct interaction	*Inflammatory response* AP-1 is a pleiotropic transcription factor involved in many biological processes including inflammation	[169]
KITLG	Kit ligand (stem cell factor)	Transcriptional activation	*Inflammatory response* Major mast cell growth factor	[170]
MGAM	Intestinal maltase-glucoamylase	Transcriptional activation	*Metabolism* Carbohydrate digestion	[93]
MGMT	O^6-methylguanine-DNA methyl-transferase	Transcriptional activation	*Metabolism* Repairs alkylated guanine in DNA; MGMT expression is reduced in patients with both type 1 and type 2 diabetes [171]	[172]
MIF	Macrophage migration inhibitory factor	Transcriptional activation	*Inflammatory response* Pro-inflammatory cytokine, counter-regulates anti-inflammatory glucocorticoid effects [98]	[97]
MYC	Myc proto-oncogene protein	Transcriptional activation	*Metabolic disease* Trigger of apoptosis in β-cells, induced by hyperglycaemia; may thus play a role in β-cell dysfunction in diabetes [173,174]	[175]
NFKBIA	NFκB inhibitor α	Transcriptional activation	*Inflammatory response* Inhibits the activity of dimeric NFκB/REL complexes by cytoplasmic sequestration	[176]
NOTCH4	Neurogenic locus notch homolog protein 4	Transcriptional activation	*Metabolic disease* A SNP in the 5′-region of NOTCH4 is associated with type 1 diabetes risk [177]; an intronic SNP is a susceptibility marker for rheumatoid arthritis [178]	[179]
PCK1	Phosphoenolpyruvate carboxykinase	Transcriptional activation	*Metabolism* Catalyzes the conversion of oxaloacetate to phosphoenolpyruvate, the rate-limiting step in gluconeogenesis	[180]
PDE4B	cAMP-specific 3′,5′-cyclic phosphodiesterase 4B	Transcriptional repression	*Inflammatory response* May be involved in mediating central nervous system effects of anti-inflammatory agents.	[93]
PIK3R1	Phosphatidylinositol 3-kinase regulatory subunit α	Binding to promoter region	*Metabolism* Necessary for the insulin-stimulated increase in glucose uptake and glycogen synthesis in insulin-sensitive tissues	[181]
PLA2G4A	Cytosolic phospholipase A2	Transcriptional activation[a]	*Inflammatory response/metabolism* Responsible for the liberation of arachidonic acid from membrane phospholipids	[182]
POMC	Pro-opiomelanocortin	Transcriptional repression	*Feedback regulation* ACTH precursor; ACTH stimulates the adrenal glands to release cortisol	[145,183]
PPARA	Peroxisome proliferator-activated receptor α	Transcriptional activation	*Metabolism* Receptor that activates the transcription of the gene for acyl-CoA oxidase and therefore controls the peroxisomal β-oxidation pathway of fatty acids	[184]
PTGS2	Prostaglandin G/H synthase 2	Transcriptional repression	*Inflammatory response/metabolism* Catalyses the formation of prostaglandin H_2 from arachidonic acid, the rate-limiting step in prostaglandin synthesis	[93]
PTPN22	Tyrosine-protein phosphatase non-receptor type 22	Transcriptional activation	*Inflammatory response/metabolic disease* A *PTPN22* SNP is associated with diabetes type 1 and inflammatory/autoimmune disorders [185]	[95]

Table 1 (*Continued*)

GR target gene	Protein name	Type of interaction	Implications in metabolism, metabolic disease and/or inflammation	References (for the interaction)
RELA	Nuclear factor NF-κB p65 subunit	Inhibition by direct interaction	*Inflammatory response* Pleiotropic transcription factor involved in many biological processes including inflammation. Crosstalk between GR and NF-κB leads to transcriptional repression of NF-κB-dependent pro-inflammatory genes as, *e.g.* *ICAM* or *TNF* (encoding intercellular adhesion molecule and TNF-α, respectively) [96]	[89]
SCNN1A	Amiloride-sensitive sodium channel subunit α	Transcriptional activation	*Metabolic syndrome* Sodium permeable non-voltage-sensitive ion channel which contributes to the regulation of blood pressure in the kidney	[186,187]
SERPINE1	Plasminogen activator inhibitor 1	Transcriptional repression	*Inflammatory response/metabolic disease* Involved in the regulation of fibrinolysis. Its overexpression correlates positively with BMI and is, among others, mediated by dietary factors and inflammatory cytokines [188]	[189]
SGK1	Serine/threonine-protein kinase Sgk1	Transcriptional activation	*Inflammatory response* Protein kinase that may contribute to hypertension and diabetic nephropathy; associates with NF-κB inhibitor kinase β leading to activation of the NF-κB pathway [190]	[88,191]
SLC10A2	Ileal sodium/bile acid cotransporter	Transcriptional activation	*Metabolism* Plays a key role in cholesterol metabolism	[192]
SPP1	Osteopontin (OPN)	Transcriptional activation	*Inflammatory disease/metabolic disease* Highly expressed in chronic inflammatory and autoimmune diseases; plays a major role in the recruitment of monocytes-macrophages, including in adipose tissue, and the regulation of cytokine production in macrophages, dendritic cells, and T-cells during the inflammatory response [103,193]	[194]
TAT	Tyrosine aminotransferase	Transcriptional activation	*Metabolism* Catalyzes the reaction of L-tyrosine and 2-oxoglutarate to 4-hydroxyphenylpyruvate and L-glutamate and thus provides gluconeogenic substrates	[195–197]
THBD	Thrombomodulin	Transcriptional activation	*Inflammatory response* Endothelial cell receptor that in a complex with thrombin activates protein C which suppresses cytokine amplification by monocytes and attenuates pro-inflammatory intracellular signalling pathways in endothelial cells [198]	[88,93]
TLR2	Toll-like receptor 2	Transcriptional activation	*Inflammatory response* Mediator of innate immune response, entailing NF-κB activation, cytokine secretion and the inflammatory response	[199]
TSC22D3	TSC22 domain family protein 3	Transcriptional activation	*Inflammatory response* Plays a role in the anti-inflammatory and immunosuppressive effects of glucocorticoids and IL-10 in macrophages	[93]

[a] Transcriptional activation of *PLA2G4A* has so far only been detected in amnion fibroblasts. The classical glucocorticoid effect on *PLA2G4A* expression is the powerful inhibition of induction by pro-inflammatory cytokines, *i.e.* the opposite effect.

Hsd11b1 expression selectively in adipose tissue of mice leads to a phenotype that faithfully mimics all symptoms of the metabolic syndrome [1]. Finally, most clinical studies showed an increase of adipose tissue *HSD11B1* expression and/or activity in human obesity (reviewed in Ref. [4]). 11β-HSD1 has thus emerged as a major potential drug target for the treatment of obesity and its associated medical conditions [4,64–69]. To date, however, the regulation of *HSD11B1* expression in adipose tissue and the mechanisms underlying the development of insulin resistance remain poorly understood. Interestingly, a recent report established a strong connection between a key player in insulin signalling, the insulin receptor substrate 1 (IRS1), and 11β-HSD1 [70]. According to the results of this study, glucocorticoid-induced insulin resistance in skeletal muscle is a result of downregulation of *IRS1* gene expression and inactivation of IRS1 protein by serine phosphorylation, which collectively leads to disruption of the insulin signalling cascade. Notably, both events are dependent on 11β-HSD1, as they could be abolished by the addition of a selective 11β-HSD1-inhibitor [70]. Another recent study explored single nucleotide polymorphisms (SNPs) in this context, but no significant correlations between common SNPs and type 2 diabetes have been found [71].

3.3. 11β-HSD1 in inflammation

At least some of the immunomodulatory effects of glucocorticoids in the inflammatory response are dependent on 11β-HSD1 activity. For instance, 11β-HSD1-deficient mice suffering from experimental arthritis exhibit a delayed resolution of the inflammatory response, in part possibly due to attenuated macrophage phagocytosis of leukocyte apoptotic bodies [8,9]. As glucocorticoids regulate both the suppression of the early and the promotion of the late phase of the inflammatory response, it is conceivable that overall deregulated, *i.e.* both decreased and increased, glucocorticoid levels could contribute to chronic inflammatory disease. Although certainly not a characteristic feature for all, some chronic inflammatory conditions indeed have been associated with increased *HSD11B1* expression, in particular inflammatory diseases of the digestive tract, *e.g.* inflammatory bowel disease and colitis [11,72–74], but also atherosclerosis [75,76] (Fig. 1). These observations are in line with numerous reports on induction of *HSD11B1* expression by the pro-inflammatory cytokines TNF-α and IL-1β in various cell types and lines including fibroblasts, adipocytes, osteoblasts and smooth muscle cells [12–14,77–85] (Table 2).

3.4. Primary GRα-target genes in metabolism and inflammation

Upregulation of 11β-HSD1 activity in adipose tissue of the obese and in inflammatory disease leads to intracellular amplification of cortisol and enhances activation of GRα, expression of which is largely unchanged under the mentioned disease conditions, as already mentioned under Section 2. In other words, the ultimate effect of *HSD11B1* overexpression is an increase in GRα-dependent regulation of gene expression. Two major mechanisms of GRα-modulated gene transcription have been investigated intensely, namely direct DNA binding and antagonism of other transcription factors by direct protein–protein interactions [86]. For regulation through direct DNA binding, the conventional view is that the GRα dimer binds palindromic glucocorticoid-response elements (GREs) in promoter regions of primary GRα target genes, leading to transactivation or transrepression. However, it should be mentioned that recent reports have shown the GRα dimerization domain to be dispensable for transactivation of some glucocorticoid-responsive genes, as *e.g. DUSP1* and *IP6K3* [87,88]. The second mechanism relies on non-classic, so-called "tethering GREs": Here, GRα does not interact with the DNA itself but binds to other transcription factors, impedes binding to the promoters of their target genes and thus opposes their action. Important examples for this type of negative transcription factor crosstalk are activator protein-1 (AP-1) and nuclear factor κB (NF-κB), which both are crucial for the inflammatory process as they induce a wide range of genes involved in inflammation [89,90]. Traditionally, the anti-inflammatory properties of glucocorticoids were to the largest part ascribed to the latter mechanism, *i.e.* antagonism of pro-inflammatory transcription factors, while glucocorticoid-induced transactivation of anti-inflammatory genes was considered to have relatively little importance for the inflammatory process. However, it becomes increasingly clear that this is not true as, in fact, several important anti-inflammatory mediators are glucocorticoid-induced [91,92]. For instance, the above mentioned *DUSP1* has only recently been shown to contribute significantly to the anti-inflammatory effects of glucocorticoids in mouse macrophages by deactivating mitogen-activated protein kinases (MAPKs), as *e.g.* p38 MAPK and c-Jun N-terminal kinase (JNK) [87].

A number of studies have been performed to identify GRα target genes at a larger scale, including some with bias towards primary target genes [88,93–95]. In order to compile these target genes we took advantage of a bioinformatic tool, the Ingenuity Pathways Analysis (www.ingenuity.com), which allows for assessing and building comprehensive molecular networks based on an extensive knowledge database. We selected only direct interactions and genes and gene products known to be implicated in metabolism and/or the inflammatory process. The results obtained were complemented and curated by manual literature research and are listed in Table 1. In efforts to confine the list to primary GRα targets we included only genes or gene products exhibiting direct interactions with GRα and GR targets derived from the above mentioned studies with bias towards the detection of primary target genes. Hence we excluded target genes known to be regulated via a tethered mechanism, as *e.g. TNF* and *ICAM1*, as they are already covered by including NF-κB as direct interaction partner into the table [96]. In total, we obtained 59 direct target genes and gene products. Of those, 24 exert functions related to the metabolic syndrome, *e.g.* hypertension (*AGT*, *HTR1A*, *SCNN1A*, and *SGK1*), hyperglycaemia (*MGAM*, *PCK1*, and *TAT*) and insulin resistance (*ANGPTL4*, *FOXO1*, *GHRHR*, *GLCCI1*, *HSD11B1*, *IGF1*, *IGFBP1*, *INSR*, *ISR1*, *MGMT*, *MYC*, *NOTCH4*, *PCK1*, *PIK3R1*, *PPARA*, *PTPN22*, and *SERPINE1*). Other affected metabolic pathways include glycosphingolipid and phospholipid synthesis (*B3GNT5* and *EKI2*), the urea cycle (*CPS1*), cholesterol, steroid, prostaglandin and xenobiotic metabolism (*CYP27A1*, *CYP2C9*, *HSD11B1*, *HSD11B2*, *PLA2G4A*, *PTGS2*, and *SLC10A2*) and the metabolism of inositol phosphates (*IP6K3*). As to genes associated with the inflammatory response, our database search yielded 28 target genes and gene products, including a subset involved in the metabolism and signal transduction of inflammatory mediators (*ALOX5P*, *GPR65*, *HSD11B1*, *HSD11B2*, *HTR1A*, *PDE4B*, *PLA2G4A*, and *PTGS2*), a subset involved in the NF-κB (*DNER*, *GCN2*, *RELA*, *NFKBIA*, and *TLR2*) and the AP-1 pathway (*JUN*), as well as chemotactic factors (*CCL2* and *CCL20*), inflammatory cytokines/cytokine receptors (*IFNB1*, *IL6*, *IL7R*, *IL8*, *IL11*, *KITLG*, and *MIF*) and a subset providing other immunomodulatory functions (*AKAP12*, *DUSP1*, *SPP1*, *THBD*, and *TSC22D3*). Notably, several target genes were found that provide glucocorticoid feedback regulation on four distinct levels: First, feedback regulation of glucocorticoid secretion under the HPA axis involves *CRH* and *POMC*. Second, augmented expression of *FKBP51* might contribute to increased cytoplasmic sequestration of the GR. Third, induction of *HSD11B2* may result in enhanced glucocorticoid inactivation and finally, the glucocorticoid-inducible gene *MIF* encodes a macrophage cytokine that counter-regulates anti-inflammatory effects of glucocorticoids such as transcriptional repression of pro-inflammatory cytokines [97,98].

Table 2
Regulation of 11β-HSD1 expression by cytokines/hormones/kinase activators/transcription factor agonists with implication in inflammatory or metabolic disease in different cell types and lines. Upwards arrows depict upregulation, downwards arrows downregulation of *HSD11B1* expression/11β-HSD1 activity.

Regulator	Implication in inflammatory or metabolic disease	Effect on *HSD11B1* expression	References
Adrenergic receptor agonists (salbutamol, clonidine)	Adrenergic receptors are targets of catecholamines (*e.g.* noradrenaline, adrenaline) and thus implicated in mobilization of energy in response to stress	↑ Activity (salbutamol) ↓ Activity (clonidine)	[78]
Eicosanoids (15-Deoxy-Δ12,14-PGJ2, prostaglandin F2α)	15-Deoxy-Δ12,14-PGJ2 is a putative (albeit disputed) endogenous PPARγ agonist [200] (also see PPARγ agonists below). Prostaglandin F2α belongs to the pro-inflammatory prostaglandins, which activate the inflammatory response	↑ Protein and activity	[14,201]
Growth hormone (GH)	Stimulates synthesis of IGF-I (see below); regulator of muscle mass and body growth	↓ Activity [109] - No effect [78]	[14,50,78,106,108–110,202–208]
Glucocorticoid receptor (GR) agonists (cortisol/corticosterone, dexamethasone)	GR regulates a multitude of genes involved in inflammation and metabolic disease (cf. Table 1). Glucocorticoids are potent inflammatory mediators, they suppress the initiation and promote the resolution of inflammation. Glucocorticoid excess can contribute to chronic inflammatory disease and leads to all symptoms of the metabolic syndrome	↑ mRNA and activity ↑↑↑ (in synergy with TNF-α/IL-1β) [85,138] ↔ Can antagonize induction by insulin	[38,75,79,80,85,107,109–112,131,132,138,204,209–215]
Interferon γ (IFN-γ)	Cytokine with important modulatory functions in the inflammatory response; potent activator of macrophages	↔ Antagonizes induction by IL-4 and IL-13	[15]
Interleukin (IL) 1α, IL-1β	Pro-inflammatory cytokine; induces acute phase reaction and fever	↑ mRNA and activity ↑↑↑ (in synergy with dexamethasone or cortisol) [85,138]	[12–15,77–81,85,109,115,138,216]
IL-4	Inflammatory cytokine with major functions in allergic inflammation	↑ mRNA and activity	[15]
IL-6	Pro-inflammatory cytokine; induces acute phase reaction	↑ Activity	[14,217]
IL-13	Anti-inflammatory cytokine; inhibits the production of macrophage inflammatory cytokines	↑ mRNA and/or activity	[15,135]
Insulin	Crucial regulator of blood sugar; increases uptake of glucose in liver, muscle, and fat tissue, stimulates glycogen synthesis and glycolysis in the liver	↓ mRNA and/or activity ↑ mRNA and activity ↔ Can antagonize induction by TNF-α	[79,82,107–112]
Insulin-like growth factor-I (IGF-I)	Crucial regulator of muscle mass; stimulates protein synthesis and inhibits protein degradation in skeletal muscle [218]	↓ Activity	[14,106]
Leptin	Regulator of body weight; controls food intake and stimulates energy expenditure, but has also pro-inflammatory functions [219]	↑ Activity	[14,220]
Liver X receptor (LXR) agonist (T0901317)	The nuclear receptor LXR, activated by oxysterols and intermediates of cholesterol biosynthesis, regulates cholesterol homeostasis and hepatic lipogenesis [125]; also modulates inflammatory signalling in macrophages by *e.g.* repressing pro-inflammatory genes [126–128]	↓ mRNA and activity	[121]
Tumor necrosis factor α (TNF-α)	Pro-inflammatory cytokine, induces acute phase reaction, activates; NF-κB and AP-1	↑ mRNA and activity ↑↑↑ (in synergy with dexamethasone or cortisol) [85,138]	[12–15,77–79,81–85,138]

Table 2 (*Continued*)

Regulator	Implication in inflammatory or metabolic disease	Effect on *HSD11B1* expression	References
PPARα agonists (fenofibrate, bezafibrate, WY14,643)	The nuclear receptor PPARα, activated by polyunsaturated and some medium-chain saturated fatty acids, regulates intracellular lipid transport and metabolism; transrepresses activities of pro-inflammatory transcription factors including NF-κB and AP-1 [127–129]	↓ mRNA	[117,123,124]
PPARγ agonists (bezafibrate, rosiglitazone, TZD2, L-805645, COOH)	PPARγ, activated by polyunsaturated fatty acids and 15-deoxy-Δ12,14-PGJ2, regulates intracellular lipid transport and metabolism; transrepresses activities of pro-inflammatory transcription factors including NF-κB and AP-1 [127–129]	↓ mRNA and activity ↑ mRNA (COOH)	[118–123]
Protein kinase A (PKA) activators (Forskolin, 8-bromo-cAMP, Dibutyryl-cAMP)	Activated by cAMP, PKA acts as a central switch from anabolic to catabolic pathways including glycolysis and β-oxidation [221–223]; also phosphorylates proteins with central functions in inflammation such as the NF-κB subunit RelA [224] and 5-lipoxygenase, an enzyme involved in the biosynthesis of leukotrienes [225]	↑ mRNA and activity [115,133] ↓ Activity [107,110]	[107,110,115,133]
Protein kinase C (PKC) activators (Phorbol 12-myristate 13-acetate, 6-[N-decylamino]-4-hydroxy-methylinole)	Activated endogenously by diacylglycerols, protein kinase C mediates inhibition of components of the insulin signalling cascade by phosphorylation, most importantly of insulin receptor substrate 1 (IRS1) [113,114]	↑ mRNA [115] ↓ Activity [116]	[115,116]
Retinoic acid, RARγ agonist ER36009	Participates in the direct and indirect regulation of a number of genes involved in inflammation and energy metabolism, including genes encoding key mediators such as IL-1β, OPN, IL-6, insulin, AP-1, leptin, PPARα, PPARγ, and more [130]	↓ mRNA and activity	[121,136]
(1,25-Dihydroxy-) Vitamin D3	Vitamin D3 may protect from type 2 diabetes; the underlying mechanisms are poorly understood [226,227]	↑ mRNA and activity	[15,228]

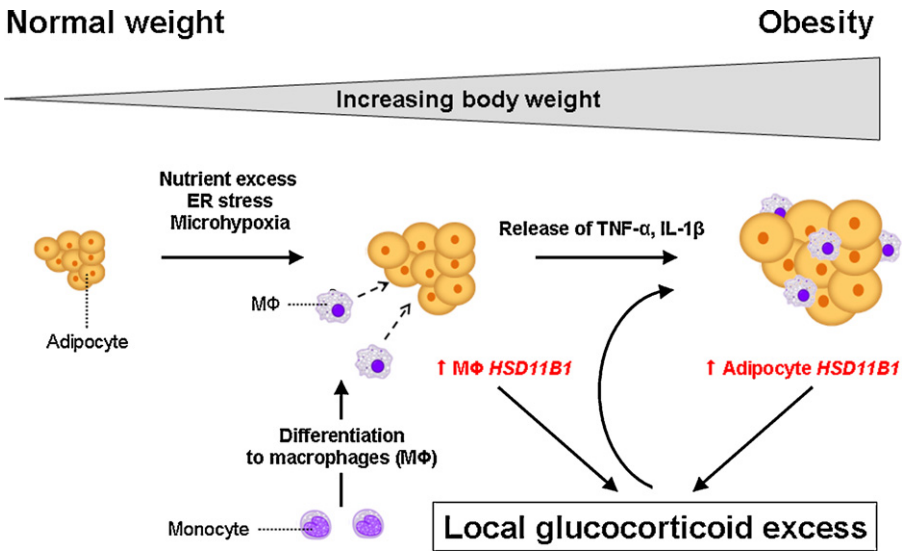

Fig. 2. Correlation between weight gain and adipose tissue levels of 11β-HSD1. In the course of weight gain, nutrient excess leads to ER stress and microhypoxia, provoking an inflammatory response which manifests itself in the recruitment of macrophages to adipose tissue. 11β-HSD1 is induced upon differentiation of monocytes to macrophages. Adipose tissue macrophages secrete pro-inflammatory cytokines, particularly TNF-α, and thus can entail induction of *HSD11B1* expression in adipocytes. Local 11β-HSD1 levels increase as a combined result of enhanced macrophage and adipocyte *HSD11B1* expression. This leads to local glucocorticoid excess which in turn can sustain and/or exacerbate obesity, reflecting a local Cushing syndrome-like effect.

3.5. 11β-HSD1 at the interface of inflammation and the metabolic syndrome

Several pieces of evidence argue for an important role of chronic "low grade" adipose tissue inflammation during the development of diet-induced visceral obesity and insulin resistance [99]. It was established more than 15 years ago that obesity is accompanied by an induction of *TNF* expression in white adipose tissue as well as an increase of systemic TNF-α protein, depletion of which leads to increased insulin sensitivity [17]. By now macrophages have been identified as the main origin of adipose tissue-secreted TNF-α and it is well acknowledged that weight gain is associated with increasing macrophage recruitment to adipose tissue [16,19,100]. *HSD11B1* gene expression is induced in monocytes during differentiation to macrophages [15] and moreover, in adipocytes and adipose stromal cells, *HSD11B1* gene expression is induced by TNF-α and IL-1β [14,78,82] and correlates strongly and positively with adipocyte size [1,101]. This increase of both macrophage and adipocyte 11β-HSD1 activity in adipose tissue probably raises local tissue and hepatic portal vein cortisol concentrations entailing a Cushing syndrome-like effect, *i.e.* inducing hyperglycaemia and insulin resistance followed by exacerbation of obesity, without affecting overall systemic glucocorticoid concentrations (Fig. 2).

Although an attractive hypothesis, it raises questions regarding the well-known immunosuppressant effects of glucocorticoids in contrast to the persistent inflammatory state in adipose tissue in obesity. Glucocorticoids repress the expression of macrophage cytokines, like TNF-α and IL-1β, and chemotactic factors like *CCL2* and *ICAM1*, both involved in macrophage recruitment to sites of inflammation. The activated glucocorticoid receptor physically interacts with two major inflammatory transcription factors, NF-κB and AP-1, counteracting induction of their target genes [89,90]. Should not visceral glucocorticoid production contribute to the resolution of the inflammatory state rather than sustain or even exacerbate it?

In fact, there are actually some inflammatory mediators expression of which is induced by glucocorticoids rather than suppressed. Two important examples are the pro-inflammatory cytokines macrophage migration inhibitory factor (MIF) and osteopontin (OPN, gene name *SPP1*) (Table 1). MIF, for instance, can override anti-inflammatory glucocorticoid effects, including the repression of *TNF*, *IL1*, *IL6* and *PTGS2* gene expression [97,98]. Similar to *HSD11B1*, *MIF* expression correlates positively with adipocyte size and hepatic insulin resistance [102]. The secreted matrix glycoprotein OPN has recently been recognized as a major determinant in macrophage infiltration of adipose tissue [103]. *SPP1*$^{-/-}$ mice fed a high-fat diet display decreased macrophage and pro-inflammatory cytokine content in adipose tissue and reduced insulin sensitivity [103]. In comparison, the gene encoding C-C motif chemokine 2 (gene name *CCL2*), repressed by cortisol, appears not to be critical in the recruitment of macrophages as *CCL2*$^{-/-}$ mice on a high-fat diet showed no reductions in adipose tissue macrophages [104]. Genes encoding other inflammatory mediators which are positively regulated by cortisol include *ALOX5AP*, an activator of leukotriene synthesis and *DNER*, an activator of NF-κB-dependent signal transduction pathways [88,93]. On the whole, it appears that cortisol can to some extent counter-balance or overrule its immunosuppressant effects by inducing other pro-inflammatory feed-forward mechanisms. This offers a possible partial explanation to the chronic low-grade nature of the inflammatory state in adipose tissue observed in obesity, but maybe chronic inflammatory states associated with increased *HSD11B1* expression in general.

3.6. Regulation of HSD11B1 expression by immunomodulatory and metabolic factors

During the last 15 years, numerous studies have assessed the regulation of *HSD11B1* expression by cytokines, hormones, kinase activators, and transcription factor agonists in mammalian cells [105]. Overall, these studies have established that *HSD11B1* expression is subject to regulation by a remarkable number of immunomodulatory and metabolic regulators (Table 2). These include a range of inflammatory cytokines, *e.g.* interferon γ (IFN-γ), interleukins IL-1, IL-4, IL-6, IL-13, and TNF-α, which, with the exception of IFN-γ, mostly upregulate *HSD11B1* expression, albeit in a highly tissue-specific manner (extensively reviewed in Ref. [105]). For instance, TNF-α and IL-1β induce *HSD11B1* expression in human adipocytes, adipose stromal cells, smooth muscle cells, osteoblasts and fibroblasts, but not in human monocytes and pri-

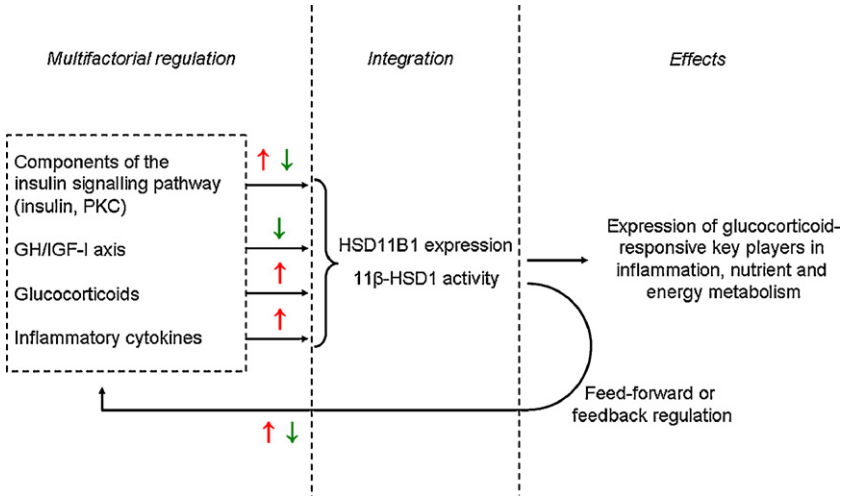

Fig. 3. 11β-HSD1 as an integrator of local metabolic and inflammatory state. Intracellular 11β-HSD1 activity is subject to regulation by multiple metabolic and inflammatory messengers, including components of the insulin signalling pathway, the GH/IGF-I axis, glucocorticoids, and inflammatory cytokines. Increased or decreased intracellular 11β-HSD1 activity leads to the corresponding change in the glucocorticoid response, with impact on the expression and activity of numerous key players in inflammation and metabolism including abundant possibilities in feed-forward or feedback mechanisms. Upwards arrows depict upregulation, downwards arrows downregulation of *HSD11B1* expression/11β-HSD1 activity. GH: growth hormone; IGF-I: insulin-like growth factor-I, and PKC: protein kinase C.

mary hepatocytes [12–15,78,80,81,85]. As to metabolic regulators, 11β-HSD1 activity is inhibited by the growth hormone/insulin-like growth factor-I (GH/IGF-I) axis in adipocytes, but again not in primary hepatocytes [14,78,106]. Diverse effects of insulin have been reported: Insulin alone may exhibit no effect, an inhibitory effect, or a stimulatory effect on *HSD11B1* expression/11β-HSD1 activity, insulin can antagonize TNF-α-mediated induction and induction by insulin can be counteracted by dexamethasone [79,82,107–112]. Activators of protein kinase C, which inhibits components of the insulin signalling cascade by phosphorylation, also variably affect 11β-HSD1 activity [113–116]. Moreover, a role of catecholamines like adrenaline and noradrenaline is likely, as adrenergic receptor agonists can modulate *HSD11B1* expression [78]. Furthermore, several key regulators of lipid metabolism and transport including peroxisome proliferator-activated receptor (PPAR)α, PPARγ, and liver X receptor (LXR) participate in the regulation of *HSD11B1* expression [117–124]. It is striking that many regulators of *HSD11B1* expression are involved in the regulation of both inflammatory and metabolic processes, as *e.g.* glucocorticoids, leptin, LXR, PPARα, PPARγ, and retinoic acid (Table 2) [125–130]. To complete the circle, many of these factors are encoded or regulated by glucocorticoid-sensitive genes, including IGF-I (encoded by *IGFI*, regulated by *IGFBP1*), growth hormone (regulated by *GHRHR*), insulin (effects mediated via *INSR* and *ISR1*), interleukin 6 (encoded by *IL6*), PPARα (encoded by *PPARA*), TNF-α (encoded by *TNF*), and, of course, 11β-HSD1 itself (cf. Table 1). Hence, a complex molecular network composed of a multitude of inflammatory and metabolic factors with abundant possibilities of feed-forward or feedback regulation mechanisms underlies the regulation of *HSD11B1* expression. 11β-HSD1 could thus act as an efficient intracellular integrator and effector of the local inflammatory and metabolic state (Fig. 3).

The underlying mechanisms for the emerging tissue-specific expression pattern are poorly understood. Relatively few studies have addressed the implicated transcription factors in cytokine-mediated induction of *HSD11B1* expression. According to these studies, CCAAT-enhancer-binding proteins (C/EBPs) appear to assume a basal role in the regulation of *HSD11B1* expression, as they contribute to TNF-α-, IL-1β-, cAMP-, and glucocorticoid-induction, the latter being additionally mediated by the GR [80,81,83,84,131–134]. Further studies suggest a significant role of the transcription factor activator protein-1 (encoded by *JUN*, see Table 1) in mediating upregulation by IL-13 and TNF-α [79,84,135]. A role for the nuclear receptors PPARα and PPARγ was suggested, as corresponding agonists affect *HSD11B1* expression [14,117–124]. Finally, retinoic acid receptor γ (RARγ) appears to mediate down-regulation of *HSD11B1* expression in response to retinoic acid or other RARγ agonists [118,136,137].

It should be noted that the studies cited in Table 2 only rarely considered the complex mixture of interacting hormones and growth factors that regulates *HSD11B1 in vivo*. Only few studies have assessed combined effects of pro-inflammatory cytokines, components of the insulin signalling pathway, and glucocorticoids. For instance, dexamethasone and insulin show no effect on *HSD11B1* expression in the hepatocyte line HuH7 when given separately, but lead to a more than two-fold induction in combination [79]. Also TNF-α/IL-1β and glucocorticoids can function in synergy to increase *HSD11B1* expression in fibroblasts and osteoblasts [79,85,138]. Therefore it is likely that studies addressing glucocorticoid-sensitive genes in the context of obesity and insulin resistance would profit from being conducted in a controlled background of TNF-α and/or insulin excess to better mimic an inflammatory state and/or hyperglycaemic conditions.

4. Conclusions

For a long time, glucocorticoid excess has been known to cause obesity. From all possible regulatory levels of glucocorticoid action including the HPA axis, intracellular GRα density, and prereceptor metabolism, the latter, in the form of the enzyme 11β-HSD1, has emerged as the most convincing determinant. 11β-HSD1 is thus nowadays recognized as a promising drug target in the current obesity epidemic. Through amplification of receptor-active glucocorticoid, 11β-HSD1 enhances the glucocorticoid response with far-ranging consequences for the expression of genes with implication in metabolic disease and inflammation. At the same time, expression of *HSD11B1* itself is subject to multifactorial control, *e.g.* by cortisol, insulin, pro-inflammatory cytokines and many more regulatory factors with central functions in inflammation and nutrient/energy metabolism. Hence, 11β-HSD1 can act as an intracellular processor of multiple metabolic and inflammatory signals and subsequently modulate both processes profoundly. In conclusion, considering the widely accepted concept of an inflammatory element in the aetiology of obesity, this enzyme is likely to play

an important causative role in the development of the metabolic syndrome at the interface of inflammation and obesity.

Acknowledgements

Work on 11β-HSD1 in our laboratory is funded by the German Federal Ministry of Education and Research (0315397A) and the Deutsche Forschungsgemeinschaft (MA 1704/5-1).

References

[1] H. Masuzaki, J. Paterson, H. Shinyama, N.M. Morton, J.J. Mullins, J.R. Seckl, J.S. Flier, A transgenic model of visceral obesity and the metabolic syndrome, Science 294 (5549) (2001) 2166–2170.
[2] J.R. Seckl, N.M. Morton, K.E. Chapman, B.R. Walker, Glucocorticoids and 11β-hydroxysteroid dehydrogenase in adipose tissue, Recent Prog. Horm. Res. 59 (2004) 359–393.
[3] B.R. Walker, R. Andrew, Tissue production of cortisol by 11β-hydroxysteroid dehydrogenase type 1 and metabolic disease, Ann. N. Y. Acad. Sci. 1083 (2006) 165–184.
[4] M. Wamil, J.R. Seckl, Inhibition of 11β-hydroxysteroid dehydrogenase type 1 as a promising therapeutic target, Drug Discov. Today 12 (13–14) (2007) 504–520.
[5] R.H. Stimson, J. Andersson, R. Andrew, D.N. Redhead, F. Karpe, P.C. Hayes, T. Olsson, B.R. Walker, Cortisol release from adipose tissue by 11β-hydroxysteroid dehydrogenase type 1 in humans, Diabetes 58 (1) (2009) 46–53.
[6] E. London, T.W. Castonguay, Diet and the role of 11β-hydroxysteroid dehydrogenase-1 on obesity, J. Nutr. Biochem. 20 (7) (2009) 485–493.
[7] N.M. Morton, J.R. Seckl, 11β-hydroxysteroid dehydrogenase type 1 and obesity, Front. Horm. Res. 36 (2008) 146–164.
[8] K.E. Chapman, A. Coutinho, M. Gray, J.S. Gilmour, J.S. Savill, J.R. Seckl, Local amplification of glucocorticoids by 11β-hydroxysteroid dehydrogenase type 1 and its role in the inflammatory response, Ann. N. Y. Acad. Sci. 1088 (2006) 265–273.
[9] J.S. Gilmour, A.E. Coutinho, J.F. Cailhier, T.Y. Man, M. Clay, G. Thomas, H.J. Harris, J.J. Mullins, J.R. Seckl, J.S. Savill, K.E. Chapman, Local amplification of glucocorticoids by 11 β-hydroxysteroid dehydrogenase type 1 promotes macrophage phagocytosis of apoptotic leukocytes, J. Immunol. 176 (12) (2006) 7605–7611.
[10] K.E. Chapman, A.E. Coutinho, M. Gray, J.S. Gilmour, J.S. Savill, J.R. Seckl, The role and regulation of 11β-hydroxysteroid dehydrogenase type 1 in the inflammatory response, Mol. Cell. Endocrinol. 301 (1–2) (2009) 123–131.
[11] J.P. Stegk, B. Ebert, H.J. Martin, E. Maser, Expression profiles of human 11β-hydroxysteroid dehydrogenases type 1 and type 2 in inflammatory bowel diseases, Mol. Cell. Endocrinol. 301 (1–2) (2009) 104–108.
[12] T.Q. Cai, B. Wong, S.S. Mundt, R. Thieringer, S.D. Wright, A. Hermanowski-Vosatka, Induction of 11β-hydroxysteroid dehydrogenase type 1 but not -2 in human aortic smooth muscle cells by inflammatory stimuli, J. Steroid Biochem. Mol. Biol. 77 (2–3) (2001) 117–122.
[13] M.S. Cooper, I. Bujalska, E. Rabbitt, E.A. Walker, R. Bland, M.C. Sheppard, M. Hewison, P.M. Stewart, Modulation of 11β-hydroxysteroid dehydrogenase isozymes by proinflammatory cytokines in osteoblasts: an autocrine switch from glucocorticoid inactivation to activation, J. Bone Miner. Res. 16 (6) (2001) 1037–1044.
[14] J.W. Tomlinson, J. Moore, M.S. Cooper, I. Bujalska, M. Shahmanesh, C. Burt, A. Strain, M. Hewison, P.M. Stewart, Regulation of expression of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue: tissue-specific induction by cytokines, Endocrinology 142 (5) (2001) 1982–1989.
[15] R. Thieringer, C.B. Le Grand, L. Carbin, T.Q. Cai, B. Wong, S.D. Wright, A. Hermanowski-Vosatka, 11 β-Hydroxysteroid dehydrogenase type 1 is induced in human monocytes upon differentiation to macrophages, J. Immunol. 167 (1) (2001) 30–35.
[16] S.P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, A.W. Ferrante Jr., Obesity is associated with macrophage accumulation in adipose tissue, J. Clin. Invest. 112 (12) (2003) 1796–1808.
[17] G.S. Hotamisligil, N.S. Shargill, B.M. Spiegelman, Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance, Science 259 (5091) (1993) 87–91.
[18] S.K. Fried, D.A. Bunkin, A.S. Greenberg, Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid, J. Clin. Endocrinol. Metab. 83 (3) (1998) 847–850.
[19] H. Xu, G.T. Barnes, Q. Yang, G. Tan, D. Yang, C.J. Chou, J. Sole, A. Nichols, J.S. Ross, L.A. Tartaglia, H. Chen, Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, J. Clin. Invest. 112 (12) (2003) 1821–1830.
[20] J. Newell-Price, X. Bertagna, A.B. Grossman, L.K. Nieman, Cushing's syndrome, Lancet 367 (9522) (2006) 1605–1617.
[21] P. Naeser, Effects of adrenalectomy on the obese-hyperglycemic syndrome in mice (gene symbol ob), Diabetologia 9 (5) (1973) 376–379.
[22] J. Burén, S.A. Bergström, E. Loh, I. Söderström, T. Olsson, C. Mattsson, Hippocampal 11β-hydroxysteroid dehydrogenase type 1 messenger ribonucleic acid expression has a diurnal variability that is lost in the obese Zucker rat, Endocrinology 148 (6) (2007) 2716–2722.
[23] N.Z. Lu, J.A. Cidlowski, The origin and functions of multiple human glucocorticoid receptor isoforms, Ann. N. Y. Acad. Sci. 1024 (2004) 102–123.
[24] T. Kino, Y.A. Su, G.P. Chrousos, Human glucocorticoid receptor isoform β: recent understanding of its potential implications in physiology and pathophysiology, Cell. Mol. Life Sci. 66 (21) (2009) 3435–3448.
[25] R.H. Oakley, M. Sar, J.A. Cidlowski, The human glucocorticoid receptor β isoform. Expression, biochemical properties, and putative function, J. Biol. Chem. 271 (16) (1996) 9550–9559.
[26] C. Gougat, D. Jaffuel, R. Gagliardo, C. Henriquet, J. Bousquet, P. Demoly, M. Mathieu, Overexpression of the human glucocorticoid receptor α and β isoforms inhibits AP-1 and NF-κB activities hormone independently, J. Mol. Med. 80 (5) (2002) 309–318.
[27] R.H. Oakley, C.M. Jewell, M.R. Yudt, D.M. Bofetiado, J.A. Cidlowski, The dominant negative activity of the human glucocorticoid receptor β isoform. Specificity and mechanisms of action, J. Biol. Chem. 274 (39) (1999) 27857–27866.
[28] M. de Castro, S. Elliot, T. Kino, C. Bamberger, M. Karl, E. Webster, G.P. Chrousos, The non-ligand binding β-isoform of the human glucocorticoid receptor (hGR β): tissue levels, mechanism of action, and potential physiologic role, Mol. Med. 2 (5) (1996) 597–607.
[29] T. Kino, I. Manoli, S. Kelkar, Y. Wang, Y.A. Su, G.P. Chrousos, Glucocorticoid receptor (GR) β has intrinsic, GRα-independent transcriptional activity, Biochem. Biophys. Res. Commun. 381 (4) (2009) 671–675.
[30] S. Boullu-Ciocca, O. Paulmyer-Lacroix, F. Fina, L. Ouafik, M.C. Alessi, C. Oliver, M. Grino, Expression of the mRNAs coding for the glucocorticoid receptor isoforms in obesity, Obes. Res. 11 (8) (2003) 925–929.
[31] W.B. Pratt, K.D. Dittmar, Studies with purified chaperones advance the understanding of the mechanism of glucocorticoid receptor-hsp90 heterocomplex assembly, Trends Endocrinol. Metab. 9 (6) (1998) 244–252.
[32] C.R. Sinars, J. Cheung-Flynn, R.A. Rimerman, J.G. Scammell, D.F. Smith, J. Clardy, Structure of the large FK506-binding protein FKBP51, an Hsp90-binding protein and a component of steroid receptor complexes, Proc. Natl. Acad. Sci. U.S.A. 100 (3) (2003) 868–873.
[33] L.M. Watts, V.P. Manchem, T.A. Leedom, A.L. Rivard, R.A. McKay, D. Bao, T. Neroladakis, B.P. Monia, D.M. Bodenmiller, J.X. Cao, H.Y. Zhang, A.L. Cox, S.J. Jacobs, M.D. Michael, K.W. Sloop, S. Bhanot, Reduction of hepatic and adipose tissue glucocorticoid receptor expression with antisense oligonucleotides improves hyperglycemia and hyperlipidemia in diabetic rodents without causing systemic glucocorticoid antagonism, Diabetes 54 (6) (2005) 1846–1853.
[34] R. Rosmond, V. Radulovic, G. Holm, A brief update of glucocorticoid receptor variants and obesity risk, Ann. N. Y. Acad. Sci. 1083 (2006) 153–164.
[35] E.F. van Rossum, S.W. Lamberts, Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition, Recent Prog. Horm. Res. 59 (2004) 333–357.
[36] R. Rosmond, The glucocorticoid receptor gene and its association to metabolic syndrome, Obes. Res. 10 (10) (2002) 1078–1086.
[37] D.J. Wake, E. Rask, D.E. Livingstone, S. Soderberg, T. Olsson, B.R. Walker, Local and systemic impact of transcriptional up-regulation of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue in human obesity, J. Clin. Endocrinol. Metab. 88 (8) (2003) 3983–3988.
[38] C.B. Whorwood, S.J. Donovan, D. Flanagan, D.I. Phillips, C.D. Byrne, Increased glucocorticoid receptor expression in human skeletal muscle cells may contribute to the pathogenesis of the metabolic syndrome, Diabetes 51 (4) (2002) 1066–1075.
[39] G. Mastorakos, M.A. Magiakou, G.P. Chrousos, Effects of the immune/inflammatory reaction on the hypothalamic–pituitary–adrenal axis, Ann. N. Y. Acad. Sci. 771 (1995) 438–448.
[40] N.A. Karrow, Activation of the hypothalamic–pituitary–adrenal axis and autonomic nervous system during inflammation and altered programming of the neuroendocrine-immune axis during fetal and neonatal development: lessons learned from the model inflammagen, lipopolysaccharide, Brain Behav. Immun. 20 (2) (2006) 144–158.
[41] M.S. Harbuz, A.J. Chover-Gonzalez, D.S. Jessop, Hypothalamo-pituitary-adrenal axis and chronic immune activation, Ann. N. Y. Acad. Sci. 992 (2003) 99–106.
[42] M. Cutolo, A. Sulli, C. Pizzorni, C. Craviotto, R.H. Straub, Hypothalamic–pituitary–adrenocortical and gonadal functions in rheumatoid arthritis, Ann. N. Y. Acad. Sci. 992 (2003) 107–117.
[43] E.F. Morand, M. Leech, Hypothalamic–pituitary–adrenal axis regulation of inflammation in rheumatoid arthritis, Immunol. Cell Biol. 79 (4) (2001) 395–399.
[44] A. Buske-Kirschbaum, S. Jobst, D.H. Hellhammer, Altered reactivity of the hypothalamus–pituitary–adrenal axis in patients with atopic dermatitis: pathologic factor or symptom? Ann. N. Y. Acad. Sci. 840 (1998) 747–754.
[45] J.A. DiBattista, J. Martel-Pelletier, T. Antakly, G. Tardif, J.M. Cloutier, J.P. Pelletier, Reduced expression of glucocorticoid receptor levels in human osteoarthritic chondrocytes. Role in the suppression of metalloprotease synthesis, J. Clin. Endocrinol. Metab. 76 (5) (1993) 1128–1134.
[46] R. Schlaghecke, E. Kornely, J. Wollenhaupt, C. Specker, Glucocorticoid receptors in rheumatoid arthritis, Arthritis Rheum. 35 (7) (1992) 740–744.
[47] G. Neeck, A. Kluter, H. Dotzlaw, M. Eggert, Involvement of the glucocorticoid receptor in the pathogenesis of rheumatoid arthritis, Ann. N. Y. Acad. Sci. 966 (2002) 491–495.

[48] D. Raddatz, P. Middel, M. Bockemuhl, P. Benohr, C. Wissmann, H. Schworer, G. Ramadori, Glucocorticoid receptor expression in inflammatory bowel disease: evidence for a mucosal down-regulation in steroid-unresponsive ulcerative colitis, Aliment. Pharmacol. Ther. 19 (1) (2004) 47–61.
[49] G. Rogler, A. Meinel, A. Lingauer, J. Michl, B. Zietz, V. Gross, B. Lang, T. Andus, J. Scholmerich, K.D. Palitzsch, Glucocorticoid receptors are down-regulated in inflamed colonic mucosa but not in peripheral blood mononuclear cells from patients with inflammatory bowel disease, Eur. J. Clin. Invest. 29 (4) (1999) 330–336.
[50] M.L. Ricketts, K.J. Shoesmith, M. Hewison, A. Strain, M.C. Eggo, P.M. Stewart, Regulation of 11 β-hydroxysteroid dehydrogenase type 1 in primary cultures of rat and human hepatocytes, J. Endocrinol. 156 (1) (1998) 159–168.
[51] E. Maser, B. Völker, J. Friebertshäuser, 11 β-Hydroxysteroid dehydrogenase type 1 from human liver: dimerization and enzyme cooperativity support its postulated role as glucocorticoid reductase, Biochemistry 41 (7) (2002) 2459–2465.
[52] A. Blum, E. Maser, Enzymology and molecular biology of glucocorticoid metabolism in humans, Prog. Nucleic Acid Res. Mol. Biol. 75 (2003) 173–216.
[53] Y.L. Zhang, X. Zhong, Z. Gjoka, Y. Li, W. Stochaj, M. Stahl, R. Kriz, J.F. Tobin, D. Erbe, V. Suri, H6PDH interacts directly with 11β-HSD1: implications for determining the directionality of glucocorticoid catalysis, Arch. Biochem. Biophys. 483 (1) (2009) 45–54.
[54] A.G. Atanasov, L.G. Nashev, L. Gelman, B. Legeza, R. Sack, R. Portmann, A. Odermatt, Direct protein–protein interaction of 11β-hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase in the endoplasmic reticulum lumen, Biochim. Biophys. Acta 1783 (8) (2008) 1536–1543.
[55] J.R. Seckl, 11 β-hydroxysteroid dehydrogenase isoforms and their implications for blood pressure regulation, Eur. J. Clin. Invest. 23 (10) (1993) 589–601.
[56] S. Nomura, M. Fujitaka, N. Sakura, K. Ueda, Circadian rhythms in plasma cortisone and cortisol and the cortisone/cortisol ratio, Clin. Chim. Acta 266 (2) (1997) 83–91.
[57] M.M. Veniant, C. Hale, R. Komorowski, M.M. Chen, D.J. St Jean, C. Fotsch, M. Wang, Time of the day for 11β-HSD1 inhibition plays a role in improving glucose homeostasis in DIO mice, Diabetes Obes. Metab. 11 (2) (2009) 109–117.
[58] J.B. Smith, G. Nolan, W. Jubiz, The relationship between unbound and total cortisol: its usefulness in detecting CBG abnormalities, Clin. Chim. Acta 108 (3) (1980) 435–445.
[59] V. Gayrard, M. Alvinerie, P.L. Toutain, Interspecies variations of corticosteroid-binding globulin parameters, Domest. Anim. Endocrinol. 13 (1) (1996) 35–45.
[60] B. Persson, Y. Kallberg, J.E. Bray, E. Bruford, S.L. Dellaporta, A.D. Favia, R.G. Duarte, H. Jornvall, K.L. Kavanagh, N. Kedishvili, M. Kisiela, E. Maser, R. Mindnich, S. Orchard, T.M. Penning, J.M. Thornton, J. Adamski, U. Oppermann, The SDR (short-chain dehydrogenase/reductase and related enzymes) nomenclature initiative, Chem. Biol. Interact. 178 (1–3) (2009) 94–98.
[61] Y. Kotelevtsev, M.C. Holmes, A. Burchell, P.M. Houston, D. Schmoll, P. Jamieson, R. Best, R. Brown, C.R. Edwards, J.R. Seckl, J.J. Mullins, 11β-hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress, Proc. Natl. Acad. Sci. U.S.A. 94 (26) (1997) 14924–14929.
[62] N.M. Morton, M.C. Holmes, C. Fievet, B. Staels, A. Tailleux, J.J. Mullins, J.R. Seckl, Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11β-hydroxysteroid dehydrogenase type 1 null mice, J. Biol. Chem. 276 (44) (2001) 41293–41300.
[63] N.M. Morton, J.M. Paterson, H. Masuzaki, M.C. Holmes, B. Staels, C. Fievet, B.R. Walker, J.S. Flier, J.J. Mullins, J.R. Seckl, Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11 β-hydroxysteroid dehydrogenase type 1-deficient mice, Diabetes 53 (4) (2004) 931–938.
[64] J.W. Tomlinson, P.M. Stewart, Mechanisms of disease: selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 as a novel treatment for the metabolic syndrome, Nat. Clin. Pract. Endocrinol. Metab. 1 (2) (2005) 92–99.
[65] J.W. Tomlinson, M. Sherlock, B. Hughes, S.V. Hughes, F. Kilvington, W. Bartlett, R. Courtney, P. Rejto, W. Carley, P.M. Stewart, Inhibition of 11β-hydroxysteroid dehydrogenase type 1 activity in vivo limits glucocorticoid exposure to human adipose tissue and decreases lipolysis, J. Clin. Endocrinol. Metab. 92 (3) (2007) 857–864.
[66] C. Hale, M. Wang, Development of 11β-HSD1 inhibitors for the treatment of type 2 diabetes, Mini Rev. Med. Chem. 8 (7) (2008) 702–710.
[67] K.A. Hughes, S.P. Webster, B.R. Walker, 11-β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors in type 2 diabetes mellitus and obesity, Expert Opin. Investig. Drugs 17 (4) (2008) 481–496.
[68] C.D. Boyle, T.J. Kowalski, 11β-hydroxysteroid dehydrogenase type 1 inhibitors: a review of recent patents, Expert Opin. Ther. Patents 19 (6) (2009) 801–825.
[69] A. Blum, A.D. Favia, E. Maser, 11β-Hydroxysteroid dehydrogenase type 1 inhibitors with oleanan and ursan scaffolds, Mol. Cell. Endocrinol. 301 (1–2) (2009) 132–136.
[70] S.A. Morgan, M. Sherlock, L.L. Gathercole, G.G. Lavery, C. Lenaghan, I.J. Bujalska, D. Laber, A. Yu, G. Convey, R. Mayers, K. Hegyi, J.K. Sethi, P.M. Stewart, D.M. Smith, J.W. Tomlinson, 11β-hydroxysteroid dehydrogenase type 1 regulates glucocorticoid-induced insulin resistance in skeletal muscle, Diabetes 58 (11) (2009) 2506–2515.
[71] Y.H. Ku, B.K. Koo, S.H. Kwak, Y.M. Cho, H.D. Shin, H.K. Lee, Y. Kim, J.W. Choi, B. Oh, K.S. Park, Regulatory effect of common promoter polymorphisms on the expression of the 11β-hydroxysteroid dehydrogenase type 1 gene, Horm. Res. 72 (1) (2009) 25–32.
[72] J. Bryndova, S. Zbankova, M. Kment, J. Pacha, Colitis up-regulates local glucocorticoid activation and down-regulates inactivation in colonic tissue, Scand. J. Gastroenterol. 39 (6) (2004) 549–553.
[73] S. Zbankova, J. Bryndova, P. Leden, M. Kment, A. Svec, J. Pacha, 11β-hydroxysteroid dehydrogenase 1 and 2 expression in colon from patients with ulcerative colitis, J. Gastroenterol. Hepatol. 22 (7) (2007) 1019–1023.
[74] P. Ergang, P. Leden, J. Bryndova, S. Zbankova, I. Miksik, M. Kment, J. Pacha, Glucocorticoid availability in colonic inflammation of rat, Dig. Dis. Sci. 53 (8) (2008) 2160–2167.
[75] M.S. Cooper, E.H. Rabbitt, P.E. Goddard, W.A. Bartlett, M. Hewison, P.M. Stewart, Osteoblastic 11β-hydroxysteroid dehydrogenase type 1 activity increases with age and glucocorticoid exposure, J. Bone Miner. Res. 17 (6) (2002) 979–986.
[76] A. Hermanowski-Vosatka, J.M. Balkovec, K. Cheng, H.Y. Chen, M. Hernandez, G.C. Koo, C.B. Le Grand, Z. Li, J.M. Metzger, S.S. Mundt, H. Noonan, C.N. Nunes, S.H. Olson, B. Pikounis, N. Ren, N. Robertson, J.M. Schaeffer, K. Shah, M.S. Springer, A.M. Strack, M. Strowski, K. Wu, T. Wu, J. Xiao, B.B. Zhang, S.D. Wright, R. Thieringer, 11β-HSD1 inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice, J. Exp. Med. 202 (4) (2005) 517–527.
[77] G. Escher, I. Galli, B.S. Vishwanath, B.M. Frey, F.J. Frey, Tumor necrosis factor α and interleukin 1β enhance the cortisone/cortisol shuttle, J. Exp. Med. 186 (2) (1997) 189–198.
[78] M. Friedberg, E. Zoumakis, N. Hiroi, T. Bader, G.P. Chrousos, Z. Hochberg, Modulation of 11 β-hydroxysteroid dehydrogenase type 1 in mature human subcutaneous adipocytes by hypothalamic messengers, J. Clin. Endocrinol. Metab. 88 (1) (2003) 385–393.
[79] Y. Iwasaki, S. Takayasu, M. Nishiyama, M. Tsugita, T. Taguchi, M. Asai, M. Yoshida, M. Kambayashi, K. Hashimoto, Is the metabolic syndrome an intracellular Cushing state? Effects of multiple humoral factors on the transcriptional activity of the hepatic glucocorticoid-activating enzyme (11β-hydroxysteroid dehydrogenase type 1) gene, Mol. Cell. Endocrinol. 285 (1–2) (2008) 10–18.
[80] Z. Yang, P. Zhu, C. Guo, X. Zhu, K. Sun, Expression of 11β-hydroxysteroid dehydrogenase type 1 in human fetal lung and regulation of its expression by interleukin-1β and cortisol, J. Clin. Endocrinol. Metab. 94 (1) (2009) 306–313.
[81] R.S. Hardy, A. Filer, M.S. Cooper, G. Parsonage, K. Raza, D.L. Hardie, E.H. Rabbitt, P.M. Stewart, C.D. Buckley, M. Hewison, Differential expression, function and response to inflammatory stimuli of 11β-hydroxysteroid dehydrogenase type 1 in human fibroblasts: a mechanism for tissue-specific regulation of inflammation, Arthritis Res. Ther. 8 (4) (2006) R108.
[82] K. Handoko, K. Yang, B. Strutt, W. Khalil, D. Killinger, Insulin attenuates the stimulatory effects of tumor necrosis factor α on 11β-hydroxysteroid dehydrogenase 1 in human adipose stromal cells, J. Steroid Biochem. Mol. Biol. 72 (3–4) (2000) 163–168.
[83] I.D. Ignatova, R.M. Kostadinova, C.E. Goldring, A.R. Nawrocki, F.J. Frey, B.M. Frey, Tumor necrosis factor-α upregulates 11β-hydroxysteroid dehydrogenase type 1 expression by CCAAT/enhancer binding protein-β in HepG2 cells, Am. J. Physiol. Endocrinol. Metab. 296 (2) (2009) E367–E377.
[84] M. Tsugita, Y. Iwasaki, M. Nishiyama, T. Taguchi, M. Shinahara, Y. Taniguchi, M. Kambayashi, Y. Terada, K. Hashimoto, Differential regulation of 11β-hydroxysteroid dehydrogenase type-1 and -2 gene transcription by proinflammatory cytokines in vascular smooth muscle cells, Life Sci. 83 (11–12) (2008) 426–432.
[85] K. Kaur, R. Hardy, M.M. Ahasan, M. Eijken, J.P. van Leeuwen, A. Filer, A.M. Thomas, K. Raza, C.D. Buckley, P.M. Stewart, E.H. Rabbitt, M. Hewison, M.S. Cooper, Synergistic induction of local glucocorticoid generation by inflammatory cytokines and glucocorticoids: implications for inflammation associated bone loss, Ann. Rheum. Dis. (2009), in press, doi:10.1136/ard.2009.107466.
[86] J.C. Webster, J.A. Cidlowski, Mechanisms of glucocorticoid-receptor-mediated repression of gene expression, Trends Endocrinol. Metab. 10 (10) (1999) 396–402.
[87] S.M. Abraham, T. Lawrence, A. Kleiman, P. Warden, M. Medghalchi, J. Tuckermann, J. Saklatvala, A.R. Clark, Antiinflammatory effects of dexamethasone are partly dependent on induction of dual specificity phosphatase 1, J. Exp. Med. 203 (8) (2006) 1883–1889.
[88] I. Rogatsky, J.C. Wang, M.K. Derynck, D.F. Nonaka, D.B. Khodabakhsh, C.M. Haqq, B.D. Darimont, M.J. Garabedian, K.R. Yamamoto, Target-specific utilization of transcriptional regulatory surfaces by the glucocorticoid receptor, Proc. Natl. Acad. Sci. U.S.A. 100 (24) (2003) 13845–13850.
[89] R.I. Scheinman, A. Gualberto, C.M. Jewell, J.A. Cidlowski, A.S. Baldwin Jr., Characterization of mechanisms involved in transrepression of NF-κ B by activated glucocorticoid receptors, Mol. Cell. Biol. 15 (2) (1995) 943–953.
[90] K. De Bosscher, W. Vanden Berghe, G. Haegeman, The interplay between the glucocorticoid receptor and nuclear factor-κB or activator protein-1: molecular mechanisms for gene repression, Endocr. Rev. 24 (4) (2003) 488–522.
[91] R. Newton, N.S. Holden, Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? Mol. Pharmacol. 72 (4) (2007) 799–809.
[92] A.R. Clark, Anti-inflammatory functions of glucocorticoid-induced genes, Mol. Cell. Endocrinol. 275 (1–2) (2007) 79–97.
[93] J.C. Wang, M.K. Derynck, D.F. Nonaka, D.B. Khodabakhsh, C. Haqq, K.R. Yamamoto, Chromatin immunoprecipitation (ChIP) scanning identifies primary glucocorticoid receptor target genes, Proc. Natl. Acad. Sci. U.S.A. 101 (44) (2004) 15603–15608.

[94] Q. Wei, E.K. Hebda-Bauer, A. Pletsch, J. Luo, M.T. Hoversten, A.J. Osetek, S.J. Evans, S.J. Watson, A.F. Seasholtz, H. Akil, Overexpressing the glucocorticoid receptor in forebrain causes an aging-like neuroendocrine phenotype and mild cognitive dysfunction, J. Neurosci. 27 (33) (2007) 8836–8844.
[95] L. Chen, C. Finnerty, W.C. Gustafson, C.R. Bush, P. Chi, H. Guo, B. Luxon, A.P. Fields, E.A. Thompson, Genomic analysis of glucocorticoid-regulated promoters in murine T-lymphoma cells, Recent Prog. Horm. Res. 58 (2003) 155–174.
[96] E. Caldenhoven, J. Liden, S. Wissink, A. Van de Stolpe, J. Raaijmakers, L. Koenderman, S. Okret, J.A. Gustafsson, P.T. Van der Saag, Negative cross-talk between RelA and the glucocorticoid receptor: a possible mechanism for the antiinflammatory action of glucocorticoids, Mol. Endocrinol. 9 (4) (1995) 401–412.
[97] T. Calandra, J. Bernhagen, C.N. Metz, L.A. Spiegel, M. Bacher, T. Donnelly, A. Cerami, R. Bucala, MIF as a glucocorticoid-induced modulator of cytokine production, Nature 377 (6544) (1995) 68–71.
[98] D. Aeberli, M. Leech, E.F. Morand, Macrophage migration inhibitory factor and glucocorticoid sensitivity, Rheumatology (Oxford) 45 (8) (2006) 937–943.
[99] H. Tilg, A.R. Moschen, Inflammatory mechanisms in the regulation of insulin resistance, Mol. Med. 14 (3–4) (2008) 222–231.
[100] R. Cancello, K. Clement, Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue, Br. J. Obstet. Gynaecol. 113 (10) (2006) 1141–1147.
[101] Z. Michailidou, M.D. Jensen, D.A. Dumesic, K.E. Chapman, J.R. Seckl, B.R. Walker, N.M. Morton, Omental 11β-hydroxysteroid dehydrogenase 1 correlates with fat cell size independently of obesity, Obesity (Silver Spring) 15 (5) (2007) 1155–1163.
[102] J. Koska, N. Stefan, S. Dubois, C. Trinidad, R.V. Considine, T. Funahashi, J.C. Bunt, E. Ravussin, P.A. Permana, mRNA concentrations of MIF in subcutaneous abdominal adipose cells are associated with adipocyte size and insulin action, Int. J. Obes. 33 (8) (2009) 842–850.
[103] T. Nomiyama, D. Perez-Tilve, D. Ogawa, F. Gizard, Y. Zhao, E.B. Heywood, K.L. Jones, R. Kawamori, L.A. Cassis, M.H. Tschop, D. Bruemmer, Osteopontin mediates obesity-induced adipose tissue macrophage infiltration and insulin resistance in mice, J. Clin. Invest. 117 (10) (2007) 2877–2888.
[104] K.E. Inouye, H. Shi, J.K. Howard, C.H. Daly, G.M. Lord, B.J. Rollins, J.S. Flier, Absence of CC chemokine ligand 2 does not limit obesity-associated infiltration of macrophages into adipose tissue, Diabetes 56 (9) (2007) 2242–2250.
[105] J.W. Tomlinson, E.A. Walker, I.J. Bujalska, N. Draper, G.G. Lavery, M.S. Cooper, M. Hewison, P.M. Stewart, 11β-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response, Endocr. Rev. 25 (5) (2004) 831–866.
[106] J.S. Moore, J.P. Monson, G. Kaltsas, P. Putignano, P.J. Wood, M.C. Sheppard, G.M. Besser, N.F. Taylor, P.M. Stewart, Modulation of 11β-hydroxysteroid dehydrogenase isozymes by growth hormone and insulin-like growth factor: in vivo and in vitro studies, J. Clin. Endocrinol. Metab. 84 (11) (1999) 4172–4177.
[107] M.M. Hammami, P.K. Siiteri, Regulation of 11 β-hydroxysteroid dehydrogenase activity in human skin fibroblasts: enzymatic modulation of glucocorticoid action, J. Clin. Endocrinol. Metab. 73 (2) (1991) 326–334.
[108] P.M. Jamieson, K.E. Chapman, C.R. Edwards, J.R. Seckl, 11 β-hydroxysteroid dehydrogenase is an exclusive 11 β-reductase in primary cultures of rat hepatocytes: effect of physicochemical and hormonal manipulations, Endocrinology 136 (11) (1995) 4754–4761.
[109] Y.J. Liu, Y. Nakagawa, K. Nasuda, H. Saegusa, Y. Igarashi, Effect of growth hormone, insulin and dexamethasone on 11 β-hydroxysteroid dehydrogenase activity on a primary culture of rat hepatocytes, Life Sci. 59 (3) (1996) 227–234.
[110] M.W. Voice, J.R. Seckl, C.R. Edwards, K.E. Chapman, 11 β-hydroxysteroid dehydrogenase type 1 expression in 2S FAZA hepatoma cells is hormonally regulated: a model system for the study of hepatic glucocorticoid metabolism, Biochem. J. 317 (Part 2) (1996) 621–625.
[111] A. Napolitano, M.W. Voice, C.R. Edwards, J.R. Seckl, K.E. Chapman, 11β-Hydroxysteroid dehydrogenase 1 in adipocytes: expression is differentiation-dependent and hormonally regulated, J. Steroid Biochem. Mol. Biol. 64 (5–6) (1998) 251–260.
[112] A. Balachandran, H. Guan, M. Sellan, S. van Uum, K. Yang, Insulin and dexamethasone dynamically regulate adipocyte 11β-hydroxysteroid dehydrogenase type 1, Endocrinology 149 (8) (2008) 4069–4079.
[113] C. Schmitz-Peiffer, T.J. Biden, Protein kinase C function in muscle, liver, and β-cells and its therapeutic implications for type 2 diabetes, Diabetes 57 (7) (2008) 1774–1783.
[114] C. Schmitz-Peiffer, Protein kinase C and lipid-induced insulin resistance in skeletal muscle, Ann. N. Y. Acad. Sci. 967 (2002) 146–157.
[115] M. Tetsuka, L.C. Haines, M. Milne, G.E. Simpson, S.G. Hillier, Regulation of 11β-hydroxysteroid dehydrogenase type 1 gene expression by LH and interleukin-1β in cultured rat granulosa cells, J. Endocrinol. 163 (3) (1999) 417–423.
[116] R.S. Ge, M.P. Hardy, Protein kinase C increases 11β-hydroxysteroid dehydrogenase oxidation and inhibits reduction in rat Leydig cells, J. Androl. 23 (1) (2002) 135–143.
[117] R.A. Srivastava, Fenofibrate ameliorates diabetic and dyslipidemic profiles in KKAy mice partly via down-regulation of 11β-HSD1, PEPCK and DGAT2. Comparison of PPARα, PPARγ, and liver x receptor agonists, Eur. J. Pharmacol. 607 (1–3) (2009) 258–263.
[118] J. Berger, M. Tanen, A. Elbrecht, A. Hermanowski-Vosatka, D.E. Moller, S.D. Wright, R. Thieringer, Peroxisome proliferator-activated receptor-γ ligands inhibit adipocyte 11β-hydroxysteroid dehydrogenase type 1 expression and activity, J. Biol. Chem. 276 (16) (2001) 12629–12635.
[119] N. Alfaidy, Z.G. Xiong, L. Myatt, S.J. Lye, J.F. MacDonald, J.R. Challis, Prostaglandin F2α potentiates cortisol production by stimulating 11β-hydroxysteroid dehydrogenase 1: a novel feedback loop that may contribute to human labor, J. Clin. Endocrinol. Metab. 86 (11) (2001) 5585–5592.
[120] M. Laplante, H. Sell, K.L. MacNaul, D. Richard, J.P. Berger, Y. Deshaies, PPAR-γ activation mediates adipose depot-specific effects on gene expression and lipoprotein lipase activity: mechanisms for modulation of postprandial lipemia and differential adipose accretion, Diabetes 52 (2) (2003) 291–299.
[121] T.M. Stulnig, U. Oppermann, K.R. Steffensen, G.U. Schuster, J.A. Gustafsson, Liver X receptors downregulate 11β-hydroxysteroid dehydrogenase type 1 expression and activity, Diabetes 51 (8) (2002) 2426–2433.
[122] D.J. Wake, R.H. Stimson, G.D. Tan, N.Z. Homer, R. Andrew, F. Karpe, B.R. Walker, Effects of peroxisome proliferator-activated receptor-α and -γ agonists on 11β-hydroxysteroid dehydrogenase type 1 in subcutaneous adipose tissue in men, J. Clin. Endocrinol. Metab. 92 (5) (2007) 1848–1856.
[123] S. Nakano, Y. Inada, H. Masuzaki, T. Tanaka, S. Yasue, T. Ishii, N. Arai, K. Ebihara, K. Hosoda, K. Maruyama, Y. Yamazaki, N. Shibata, K. Nakao, Bezafibrate regulates the expression and enzyme activity of 11β-hydroxysteroid dehydrogenase type 1 in murine adipose tissue and 3T3-L1 adipocytes, Am. J. Physiol. Endocrinol. Metab. 292 (4) (2007) E1213–E1222.
[124] A. Hermanowski-Vosatka, D. Gerhold, S.S. Mundt, V.A. Loving, M. Lu, Y. Chen, A. Elbrecht, M. Wu, T. Doebber, L. Kelly, D. Milot, Q. Guo, P.R. Wang, M. Ippolito, Y.S. Chao, S.D. Wright, R. Thieringer, PPARα agonists reduce 11β-hydroxysteroid dehydrogenase type 1 in the liver, Biochem. Biophys. Res. Commun. 279 (2) (2000) 330–336.
[125] G. Wojcicka, A. Jamroz-Wisniewska, K. Horoszewicz, J. Beltowski, Liver X receptors (LXRs). Part I: Structure, function, regulation of activity, and role in lipid metabolism, Postepy Hig. Med. Dosw. 61 (2007) 736–759.
[126] N. Zelcer, P. Tontonoz, Liver X receptors as integrators of metabolic and inflammatory signaling, J. Clin. Invest. 116 (3) (2006) 607–614.
[127] E. Rigamonti, G. Chinetti-Gbaguidi, B. Staels, Regulation of macrophage functions by PPAR-α, PPAR-γ, and LXRs in mice and men, Arterioscler. Thromb. Vasc. Biol. 28 (6) (2008) 1050–1059.
[128] C. Hong, P. Tontonoz, Coordination of inflammation and metabolism by PPAR and LXR nuclear receptors, Curr. Opin. Genet. Dev. 18 (5) (2008) 461–467.
[129] R.A. Daynes, D.C. Jones, Emerging roles of PPARs in inflammation and immunity, Nat. Rev. Immunol. 2 (10) (2002) 748–759.
[130] J.E. Balmer, R. Blomhoff, Gene expression regulation by retinoic acid, J. Lipid Res. 43 (11) (2002) 1773–1808.
[131] S. Sai, C.L. Esteves, V. Kelly, Z. Michailidou, K. Anderson, A.P. Coll, Y. Nakagawa, T. Ohzeki, J.R. Seckl, K.E. Chapman, Glucocorticoid regulation of the promoter of 11β-hydroxysteroid dehydrogenase type 1 is indirect and requires CCAAT/enhancer-binding protein-β, Mol. Endocrinol. 22 (9) (2008) 2049–2060.
[132] Z. Yang, C. Guo, P. Zhu, W. Li, L. Myatt, K. Sun, Role of glucocorticoid receptor and CCAAT/enhancer-binding protein α in the feed-forward induction of 11β-hydroxysteroid dehydrogenase type 1 expression by cortisol in human amnion fibroblasts, J. Endocrinol. 195 (2) (2007) 241–253.
[133] J. Gout, J. Tirard, C. Thevenon, J.P. Riou, M. Begeot, D. Naville, CCAAT/enhancer-binding proteins (C/EBPs) regulate the basal and cAMP-induced transcription of the human 11β-hydroxysteroid dehydrogenase encoding gene in adipose cells, Biochimie 88 (9) (2006) 1115–1124.
[134] P.B. Hebbar, T.K. Archer, Chromatin-dependent cooperativity between site-specific transcription factors in vivo, J. Biol. Chem. 282 (11) (2007) 8284–8291.
[135] A. Hu, S. Fatma, J. Cao, J.S. Grunstein, G. Nino, Y. Grumbach, M.M. Grunstein, Th2 cytokine-induced upregulation of 11β-hydroxysteroid dehydrogenase-1 facilitates glucocorticoid suppression of proasthmatic airway smooth muscle function, Am. J. Physiol. Lung Cell. Mol. Physiol. 296 (5) (2009) L790–803.
[136] E.M. Aubry, A. Odermatt, Retinoic acid reduces glucocorticoid sensitivity in C2C12 myotubes by decreasing 11β-hydroxysteroid dehydrogenase type 1 and glucocorticoid receptor activities, Endocrinology 150 (6) (2009) 2700–2708.
[137] T. Sakuta, T. Uchiyama, T. Kanayama, Topical ER36009, a RARγ-selective retinoid, decreases abdominal white adipose tissue and elicits changes in expression of genes related to adiposity and thermogenesis, Endocrine 30 (1) (2006) 113–119.
[138] K. Sun, L. Myatt, Enhancement of glucocorticoid-induced 11β-hydroxysteroid dehydrogenase type 1 expression by proinflammatory cytokines in cultured human amnion fibroblasts, Endocrinology 144 (12) (2003) 5568–5577.
[139] A.R. Brasier, J.E. Tate, D. Ron, J.F. Habener, Multiple cis-acting DNA regulatory elements mediate hepatic angiotensinogen gene expression, Mol. Endocrinol. 3 (6) (1989) 1022–1034.
[140] M. Yan, C. Xia, C. Cheng, X. Shao, S. Niu, H. Liu, A. Shen, The role of TNF-α and its receptors in the production of Src-suppressed C kinase substrate by rat primary type-2 astrocytes, Brain Res. 1184 (2007) 28–37.
[141] L. Boring, J. Gosling, S.W. Chensue, S.L. Kunkel, R.V. Farese Jr., H.E. Broxmeyer, I.F. Charo, Impaired monocyte migration and reduced type 1 (Th1) cytokine responses in C-C chemokine receptor 2 knockout mice, J. Clin. Invest. 100 (10) (1997) 2552–2561.
[142] B.J. Rollins, A. Walz, M. Baggiolini, Recombinant human MCP-1/JE induces chemotaxis, calcium flux, and the respiratory burst in human monocytes, Blood 78 (4) (1991) 1112–1116.
[143] P. Sartipy, D.J. Loskutoff, Monocyte chemoattractant protein 1 in obesity and insulin resistance, Proc. Natl. Acad. Sci. U.S.A. 100 (12) (2003) 7265–7270.

[144] V.M. Christoffels, T. Grange, K.H. Kaestner, T.J. Cole, G.J. Darlington, C.M. Croniger, W.H. Lamers, Glucocorticoid receptor, C/EBP, HNF3, and protein kinase A coordinately activate the glucocorticoid response unit of the carbamoylphosphate synthetase I gene, Mol. Cell. Biol. 18 (11) (1998) 6305–6315.
[145] H.M. Reichardt, T. Umland, A. Bauer, O. Kretz, G. Schutz, Mice with an increased glucocorticoid receptor gene dosage show enhanced resistance to stress and endotoxic shock, Mol. Cell. Biol. 20 (23) (2000) 9009–9017.
[146] S.P. Malkoski, R.I. Dorin, Composite glucocorticoid regulation at a functionally defined negative glucocorticoid response element of the human corticotropin-releasing hormone gene, Mol. Endocrinol. 13 (10) (1999) 1629–1644.
[147] J. Mullick, H.K. Anandatheerthavarada, G. Amuthan, S.V. Bhagwat, G. Biswas, V. Camasamudram, N.K. Bhat, S.E. Reddy, V. Rao, N.G. Avadhani, Physical interaction and functional synergy between glucocorticoid receptor and Ets2 proteins for transcription activation of the rat cytochrome P-450c27 promoter, J. Biol. Chem. 276 (21) (2001) 18007–18017.
[148] S. Gerbal-Chaloin, M. Daujat, J.M. Pascussi, L. Pichard-Garcia, M.J. Vilarem, P. Maurel, Transcriptional regulation of CYP2C9 gene. Role of glucocorticoid receptor and constitutive androstane receptor, J. Biol. Chem. 277 (1) (2002) 209–217.
[149] T. Kino, E. Souvatzoglou, E. Charmandari, T. Ichijo, P. Driggers, C. Mayers, A. Alatsatianos, I. Manoli, H. Westphal, G.P. Chrousos, J.H. Segars, Rho family Guanine nucleotide exchange factor Brx couples extracellular signals to the glucocorticoid signaling system, J. Biol. Chem. 281 (14) (2006) 9118–9126.
[150] H.Y. Jiang, S.A. Wek, B.C. McGrath, D. Scheuner, R.J. Kaufman, D.R. Cavener, R.C. Wek, Phosphorylation of the α subunit of eukaryotic initiation factor 2 is required for activation of NF-κB in response to diverse cellular stresses, Mol. Cell. Biol. 23 (16) (2003) 5651–5663.
[151] H. Nogami, Y. Hiraoka, M. Matsubara, E. Nonobe, T. Harigaya, M. Katayama, N. Hemmi, S. Kobayashi, K. Mogi, S. Aiso, K. Kawamura, S. Hisano, A composite hormone response element regulates transcription of the rat GHRH receptor gene, Endocrinology 143 (4) (2002) 1318–1326.
[152] M.S. Chapman, D.J. Askew, U. Kuscuoglu, R.L. Miesfeld, Transcriptional control of steroid-regulated apoptosis in murine thymoma cells, Mol. Endocrinol. 10 (8) (1996) 967–978.
[153] P. Formichi, E. Radi, C. Battisti, A. Pasqui, G. Pompella, P.E. Lazzerini, F. Laghi-Pasini, A. Leonini, A. Di Stefano, A. Federico, Psychosine-induced apoptosis and cytokine activation in immune peripheral cells of Krabbe patients, J. Cell. Physiol. 212 (3) (2007) 737–743.
[154] R. Alikhani-Koupaei, F. Fouladkou, P. Fustier, B. Cenni, A.M. Sharma, H.C. Deter, B.M. Frey, F.J. Frey, Identification of polymorphisms in the human 11β-hydroxysteroid dehydrogenase type 2 gene promoter: functional characterization and relevance for salt sensitivity, FASEB J. 21 (13) (2007) 3618–3628.
[155] X.M. Ou, J.M. Storring, N. Kushwaha, P.R. Albert, Heterodimerization of mineralocorticoid and glucocorticoid receptors at a novel negative response element of the 5-HT1A receptor gene, J. Biol. Chem. 276 (17) (2001) 14299–14307.
[156] B. Soury, D. Hentzen, M. Vignal, N. Christeff, J. Doly, Induction of interferon-β gene expression by dexamethasone in murine L929 cells, Mol. Endocrinol. 9 (2) (1995) 199–207.
[157] F. Tronche, C. Opherk, R. Moriggl, C. Kellendonk, A. Reimann, L. Schwake, H.M. Reichardt, K. Stangl, D. Gau, A. Hoeflich, H. Beug, W. Schmid, G. Schutz, Glucocorticoid receptor function in hepatocytes is essential to promote postnatal body growth, Genes Dev. 18 (5) (2004) 492–497.
[158] R. Goswami, R. Lacson, E. Yang, R. Sam, T. Unterman, Functional analysis of glucocorticoid and insulin response sequences in the rat insulin-like growth factor-binding protein-1 promoter, Endocrinology 134 (2) (1994) 736–743.
[159] G. Schweizer-Groyer, N. Jibard, E. Neau, D. Fortin, F. Cadepond, E.E. Baulieu, A. Groyer, The glucocorticoid response element II is functionally homologous in rat and human insulin-like growth factor-binding protein-1 promoters, J. Biol. Chem. 274 (17) (1999) 11679–11686.
[160] A. Ray, K.S. LaForge, P.B. Sehgal, On the mechanism for efficient repression of the interleukin-6 promoter by glucocorticoids: enhancer, TATA box, and RNA start site (Inr motif) occlusion, Mol. Cell. Biol. 10 (11) (1990) 5736–5746.
[161] A. Ray, K.S. LaForge, P.B. Sehgal, Repressor to activator switch by mutations in the first Zn finger of the glucocorticoid receptor: is direct DNA binding necessary? Proc. Natl. Acad. Sci. U.S.A. 88 (16) (1991) 7086–7090.
[162] S. Sallmann, E. Juttler, S. Prinz, N. Petersen, U. Knopf, T. Weiser, M. Schwaninger, Induction of interleukin-6 by depolarization of neurons, J. Neurosci. 20 (23) (2000) 8637–8642.
[163] H.C. Lee, H. Shibata, S. Ogawa, K. Maki, K. Ikuta, Transcriptional regulation of the mouse IL-7 receptor α promoter by glucocorticoid receptor, J. Immunol. 174 (12) (2005) 7800–7806.
[164] H. Garside, A. Stevens, S. Farrow, C. Normand, B. Houle, A. Berry, B. Maschera, D. Ray, Glucocorticoid ligands specify different interactions with NF-κB by allosteric effects on the glucocorticoid receptor DNA binding domain, J. Biol. Chem. 279 (48) (2004) 50050–50059.
[165] N.Z. Lu, J.B. Collins, S.F. Grissom, J.A. Cidlowski, Selective regulation of bone cell apoptosis by translational isoforms of the glucocorticoid receptor, Mol. Cell. Biol. 27 (20) (2007) 7143–7160.
[166] J.K. Lee, S.Y. Tsai, Multiple hormone response elements can confer glucocorticoid regulation on the human insulin receptor gene, Mol. Endocrinol. 8 (5) (1994) 625–634.
[167] S.B. Shears, Diphosphoinositol polyphosphates: metabolic messengers? Mol. Pharmacol. 76 (2) (2009) 236–252.
[168] M.A. Turnbow, S.R. Keller, K.M. Rice, C.W. Garner, Dexamethasone down-regulation of insulin receptor substrate-1 in 3T3-L1 adipocytes, J. Biol. Chem. 269 (4) (1994) 2516–2520.
[169] H.F. Yang-Yen, J.C. Chambard, Y.L. Sun, T. Smeal, T.J. Schmidt, J. Drouin, M. Karin, Transcriptional interference between c-Jun and the glucocorticoid receptor: mutual inhibition of DNA binding due to direct protein–protein interaction, Cell 62 (6) (1990) 1205–1215.
[170] C.A. Da Silva, C. Heilbock, O. Kassel, N. Frossard, Transcription of stem cell factor (SCF) is potentiated by glucocorticoids and interleukin-1β through concerted regulation of a GRE-like and an NF-κB response element, FASEB J. 17 (15) (2003) 2334–2336.
[171] T. Akcay, Y. Dincer, N. Celebi, H. Ilkova, O(6)-methylguanine DNA methyltransferase activity in diabetic patients, Diabetes Res. Clin. Pract. 61 (1) (2003) 1–6.
[172] T. Biswas, C.V. Ramana, G. Srinivasan, I. Boldogh, T.K. Hazra, Z. Chen, K. Tano, E.B. Thompson, S. Mitra, Activation of human O^6-methylguanine-DNA methyltransferase gene by glucocorticoid hormone, Oncogene 18 (2) (1999) 525–532.
[173] S. Pelengaris, M. Khan, G.I. Evan, Suppression of Myc-induced apoptosis in β cells exposes multiple oncogenic properties of Myc and triggers carcinogenic progression, Cell 109 (3) (2002) 321–334.
[174] S. Pelengaris, M. Khan, The many faces of c-MYC, Arch. Biochem. Biophys. 416 (2) (2003) 129–136.
[175] T. Ma, J.A. Copland, A.R. Brasier, E.A. Thompson, A novel glucocorticoid receptor binding element within the murine c-myc promoter, Mol. Endocrinol. 14 (9) (2000) 1377–1386.
[176] B.J. Deroo, T.K. Archer, Glucocorticoid receptor activation of the I κ B α promoter within chromatin, Mol. Biol. Cell 12 (11) (2001) 3365–3374.
[177] A.M. Valdes, G. Thomson, Several loci in the HLA class III region are associated with T1D risk after adjusting for DRB1-DQB1, Diabetes Obes. Metab. 11 (Suppl. 1) (2009) 46–52.
[178] Y. Kochi, R. Yamada, K. Kobayashi, A. Takahashi, A. Suzuki, A. Sekine, A. Mabuchi, F. Akiyama, T. Tsunoda, Y. Nakamura, K. Yamamoto, Analysis of single-nucleotide polymorphisms in Japanese rheumatoid arthritis patients shows additional susceptibility markers besides the classic shared epitope susceptibility sequences, Arthritis Rheum. 50 (1) (2004) 63–71.
[179] J. Wu, E.H. Bresnick, Glucocorticoid and growth factor synergism requirement for Notch4 chromatin domain activation, Mol. Cell. Biol. 27 (6) (2007) 2411–2422.
[180] J.M. Stafford, M. Waltner-Law, D.K. Granner, Role of accessory factors and steroid receptor coactivator 1 in the regulation of phosphoenolpyruvate carboxykinase gene transcription by glucocorticoids, J. Biol. Chem. 276 (6) (2001) 3811–3819.
[181] L.L. Wang, C.C. Ou, J.Y. Chan, Receptor-independent activation of GABAergic neurotransmission and receptor-dependent nontranscriptional activation of phosphatidylinositol 3-kinase/protein kinase Akt pathway in short-term cardiovascular actions of dexamethasone at the nucleus tractus solitarii of the rat, Mol. Pharmacol. 67 (2) (2005) 489–498.
[182] C. Guo, Z. Yang, W. Li, P. Zhu, L. Myatt, K. Sun, Paradox of glucocorticoid-induced cytosolic phospholipase A2 group IVA messenger RNA expression involves glucocorticoid receptor binding to the promoter in human amnion fibroblasts, Biol. Reprod. 78 (1) (2008) 193–197.
[183] N. Radoja, M. Komine, S.H. Jho, M. Blumenberg, M. Tomic-Canic, Novel mechanism of steroid action in skin through glucocorticoid receptor monomers, Mol. Cell. Biol. 20 (12) (2000) 4328–4339.
[184] G.A. Francis, E. Fayard, F. Picard, J. Auwerx, Nuclear receptors and the control of metabolism, Annu. Rev. Physiol. 65 (2003) 261–311.
[185] T. Vang, M. Congia, M.D. Macis, L. Musumeci, V. Orru, P. Zavattari, K. Nika, L. Tautz, K. Tasken, F. Cucca, T. Mustelin, N. Bottini, Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant, Nat. Genet. 37 (12) (2005) 1317–1319.
[186] H.C. Wang, M.D. Zentner, H.T. Deng, K.J. Kim, R. Wu, P.C. Yang, D.K. Ann, Oxidative stress disrupts glucocorticoid hormone-dependent transcription of the amiloride-sensitive epithelial sodium channel α-subunit in lung epithelial cells through ERK-dependent and thioredoxin-sensitive pathways, J. Biol. Chem. 275 (12) (2000) 8600–8609.
[187] R. Sayegh, S.D. Auerbach, X. Li, R.W. Loftus, R.F. Husted, J.B. Stokes, C.P. Thomas, Glucocorticoid induction of epithelial sodium channel expression in lung and renal epithelia occurs via trans-activation of a hormone response element in the 5′-flanking region of the human epithelial sodium channel α subunit gene, J. Biol. Chem. 274 (18) (1999) 12431–12437.
[188] T. Skurk, H. Hauner, Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1, Int. J. Obes. Relat. Metab. Disord. 28 (11) (2004) 1357–1364.
[189] C.J. Bruzdzinski, M.R. Johnson, C.A. Goble, S.S. Winograd, T.D. Gelehrter, Mechanism of glucocorticoid induction of the rat plasminogen activator inhibitor-1 gene in HTC rat hepatoma cells: identification of cis-acting regulatory elements, Mol. Endocrinol. 7 (9) (1993) 1169–1177.
[190] L. Zhang, R. Cui, X. Cheng, J. Du, Antiapoptotic effect of serum and glucocorticoid-inducible protein kinase is mediated by novel mechanism activating IκB kinase, Cancer Res. 65 (2) (2005) 457–464.
[191] A.C. Maiyar, P.T. Phu, A.J. Huang, G.L. Firestone, Repression of glucocorticoid receptor transactivation and DNA binding of a glucocorticoid response element within the serum/glucocorticoid-inducible protein kinase (sgk) gene

promoter by the p53 tumor suppressor protein, Mol. Endocrinol. 11 (3) (1997) 312–329.
[192] G.A. Kullak-Ublick, B. Stieger, P.J. Meier, Enterohepatic bile salt transporters in normal physiology and liver disease, Gastroenterology 126 (1) (2004) 322–342.
[193] M. Scatena, L. Liaw, C.M. Giachelli, Osteopontin: a multifunctional molecule regulating chronic inflammation and vascular disease, Arterioscler. Thromb. Vasc. Biol. 27 (11) (2007) 2302–2309.
[194] D. Wang, S. Yamamoto, N. Hijiya, E.N. Benveniste, C.L. Gladson, Transcriptional regulation of the human osteopontin promoter: functional analysis and DNA–protein interactions, Oncogene 19 (50) (2000) 5801–5809.
[195] G. Srinivasan, N.T. Patel, E.B. Thompson, Heat shock protein is tightly associated with the recombinant human glucocorticoid receptor:glucocorticoid response element complex, Mol. Endocrinol. 8 (2) (1994) 189–196.
[196] D.K. Scott, P.E. Stromstedt, J.C. Wang, D.K. Granner, Further characterization of the glucocorticoid response unit in the phosphoenolpyruvate carboxykinase gene. The role of the glucocorticoid receptor-binding sites, Mol. Endocrinol. 12 (4) (1998) 482–491.
[197] S. Pandit, W. Geissler, G. Harris, A. Sitlani, Allosteric effects of dexamethasone and RU486 on glucocorticoid receptor–DNA interactions, J. Biol. Chem. 277 (2) (2002) 1538–1543.
[198] H. Weiler, B.H. Isermann, Thrombomodulin, J. Thromb. Haemost. 1 (7) (2003) 1515–1524.
[199] M.A. Hermoso, T. Matsuguchi, K. Smoak, J.A. Cidlowski, Glucocorticoids and tumor necrosis factor α cooperatively regulate toll-like receptor 2 gene expression, Mol. Cell. Biol. 24 (11) (2004) 4743–4756.
[200] W.S. Powell, 15-Deoxy-Δ12,14-PGJ2: endogenous PPARγ ligand or minor eicosanoid degradation product? J. Clin. Invest. 112 (6) (2003) 828–830.
[201] H.Y. Lee, T.J. Acosta, D.J. Skarzynski, K. Okuda, Prostaglandin F2α stimulates 11β-Hydroxysteroid dehydrogenase 1 enzyme bioactivity and protein expression in bovine endometrial stromal cells, Biol. Reprod. 80 (4) (2009) 657–664.
[202] A. Agha, J.P. Monson, Modulation of glucocorticoid metabolism by the growth hormone – IGF-1 axis, Clin. Endocrinol. (Oxf.) 66 (4) (2007) 459–465.
[203] S.C. Low, K.E. Chapman, C.R. Edwards, T. Wells, I.C. Robinson, J.R. Seckl, Sexual dimorphism of hepatic 11 β-hydroxysteroid dehydrogenase in the rat: the role of growth hormone patterns, J. Endocrinol. 143 (3) (1994) 541–548.
[204] H.B. Gao, R.S. Ge, V. Lakshmi, A. Marandici, M.P. Hardy, Hormonal regulation of oxidative and reductive activities of 11 β-hydroxysteroid dehydrogenase in rat Leydig cells, Endocrinology 138 (1) (1997) 156–161.
[205] S.K. Paulsen, S.B. Pedersen, J.O. Jorgensen, S. Fisker, J.S. Christiansen, A. Flyvbjerg, B. Richelsen, Growth hormone (GH) substitution in GH-deficient patients inhibits 11β-hydroxysteroid dehydrogenase type 1 messenger ribonucleic acid expression in adipose tissue, J. Clin. Endocrinol. Metab. 91 (3) (2006) 1093–1098.
[206] S.V. Gelding, N.F. Taylor, P.J. Wood, K. Noonan, J.U. Weaver, D.F. Wood, J.P. Monson, The effect of growth hormone replacement therapy on cortisol-cortisone interconversion in hypopituitary adults: evidence for growth hormone modulation of extrarenal 11 β-hydroxysteroid dehydrogenase activity, Clin. Endocrinol. (Oxf.) 48 (2) (1998) 153–162.
[207] P.J. Trainer, W.M. Drake, L.A. Perry, N.F. Taylor, G.M. Besser, J.P. Monson, Modulation of cortisol metabolism by the growth hormone receptor antagonist pegvisomant in patients with acromegaly, J. Clin. Endocrinol. Metab. 86 (7) (2001) 2989–2992.
[208] A.A. Toogood, N.F. Taylor, S.M. Shalet, J.P. Monson, Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients, J. Clin. Endocrinol. Metab. 85 (4) (2000) 1727–1730.
[209] I.J. Bujalska, S. Kumar, P.M. Stewart, Does central obesity reflect "Cushing's disease of the omentum"? Lancet 349 (9060) (1997) 1210–1213.
[210] J.W. Tomlinson, B. Sinha, I. Bujalska, M. Hewison, P.M. Stewart, Expression of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue is not increased in human obesity, J. Clin. Endocrinol. Metab. 87 (12) (2002) 5630–5635.
[211] S. Gupta, N. Alfaidy, A.C. Holloway, W.L. Whittle, S.J. Lye, W. Gibb, J.R. Challis, Effects of cortisol and oestradiol on hepatic 11β-hydroxysteroid dehydrogenase type 1 and glucocorticoid receptor proteins in late-gestation sheep fetus, J. Endocrinol. 176 (2) (2003) 175–184.
[212] K.H. Nwe, A. Hamid, P.B. Morat, B.A. Khalid, Differential regulation of the oxidative 11β-hydroxysteroid dehydrogenase activity in testis and liver, Steroids 65 (1) (2000) 40–45.
[213] P.M. Jamieson, K.E. Chapman, J.R. Seckl, Tissue- and temporal-specific regulation of 11β-hydroxysteroid dehydrogenase type 1 by glucocorticoids in vivo, J. Steroid Biochem. Mol. Biol. 68 (5–6) (1999) 245–250.
[214] M.P. Moisan, J.R. Seckl, C.R. Edwards, 11 β-hydroxysteroid dehydrogenase bioactivity and messenger RNA expression in rat forebrain: localization in hypothalamus, hippocampus, and cortex, Endocrinology 127 (3) (1990) 1450–1455.
[215] K. Sun, P. He, K. Yang, Intracrine induction of 11β-hydroxysteroid dehydrogenase type 1 expression by glucocorticoid potentiates prostaglandin production in the human chorionic trophoblast, Biol. Reprod. 67 (5) (2002) 1450–1455.
[216] P.Y. Yong, C. Harlow, K.J. Thong, S.G. Hillier, Regulation of 11β-hydroxysteroid dehydrogenase type 1 gene expression in human ovarian surface epithelial cells by interleukin-1, Hum. Reprod. 17 (9) (2002) 2300–2306.
[217] M. Evagelatou, S.L. Peterson, B.A. Cooke, Leukocytes modulate 11β-hydroxysteroid dehydrogenase (11β-HSD) activity in human granulosa-lutein cell cultures, Mol. Cell. Endocrinol. 133 (2) (1997) 81–88.
[218] C.P. Velloso, Regulation of muscle mass by growth hormone and IGF-I, Br. J. Pharmacol. 154 (3) (2008) 557–568.
[219] M. Otero, R. Lago, F. Lago, F.F. Casanueva, C. Dieguez, J.J. Gomez-Reino, O. Gualillo, Leptin, from fat to inflammation: old questions and new insights, FEBS Lett. 579 (2) (2005) 295–301.
[220] Y. Liu, Y. Nakagawa, Y. Wang, R. Li, X. Li, T. Ohzeki, T.C. Friedman, Leptin activation of corticosterone production in hepatocytes may contribute to the reversal of obesity and hyperglycemia in leptin-deficient ob/ob mice, Diabetes 52 (6) (2003) 1409–1416.
[221] B.E. Kemp, D. Stapleton, D.J. Campbell, Z.P. Chen, S. Murthy, M. Walter, A. Gupta, J.J. Adams, F. Katsis, B. van Denderen, I.G. Jennings, T. Iseli, B.J. Michell, L.A. Witters, AMP-activated protein kinase, super metabolic regulator, Biochem. Soc. Trans. 31 (Part 1) (2003) 162–168.
[222] M.C. Towler, D.G. Hardie, AMP-activated protein kinase in metabolic control and insulin signaling, Circ. Res. 100 (3) (2007) 328–341.
[223] P. Misra, R. Chakrabarti, The role of AMP kinase in diabetes, Indian J. Med. Res. 125 (3) (2007) 389–398.
[224] S.K. Manna, C. Gangadharan, Decrease in RelA phosphorylation by inhibiting protein kinase A induces cell death in NF-κB-expressing and drug-resistant tumor cells, Mol. Immunol. 46 (7) (2009) 1340–1350.
[225] M. Luo, S.M. Jones, S.M. Phare, M.J. Coffey, M. Peters-Golden, T.G. Brock, Protein kinase A inhibits leukotriene synthesis by phosphorylation of 5-lipoxygenase on serine 523, J. Biol. Chem. 279 (40) (2004) 41512–41520.
[226] G. Rammos, P. Tseke, S. Ziakka, Vitamin D, the rennin–angiotensin system, and insulin resistance, Int. Urol. Nephrol. 40 (2) (2008) 419–426.
[227] L.G. Danescu, S. Levy, J. Levy, Vitamin D and diabetes mellitus, Endocrine 35 (1) (2009) 11–17.
[228] K.L. Morris, M.B. Zemel, 1,25-dihydroxyvitamin D3 modulation of adipocyte glucocorticoid function, Obes. Res. 13 (4) (2005) 670–677.