Adrenocortical dysregulation as a major player in insulin resistance and onset of obesity

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Roberge C, Carpentier AC, Langlois M-F, Baillargeon J-P, Ardilouze J-L, Maheux P, Gallo-Payet N. Adrenocortical dysregulation as a major player in insulin resistance and onset of obesity. Am J Physiol Endocrinol Metab 293: E1465–E1478, 2007. First published October 2, 2007; doi:10.1152/ajpendo.00516.2007.—The aim of this review is to explore the dysregulation of adrenocortical secretions as a major contributor in the development of obesity and insulin resistance. Disturbance of adipose tissue physiology is one of the primary events in the development of pathologies associated with the metabolic syndrome, such as obesity and type 2 diabetes. Several studies indicate that alterations in metabolism of glucocorticoids (GC) and androgens, as well as aldosterone in excess, are involved in the emergence of metabolic syndrome. Cross talk among adipose tissue, the hypothalamo-pituitary complex, and adrenal gland activity plays a major role in the control of food intake, glucose metabolism, lipid storage, and energy balance. Perturbation of this cross talk induces alterations in the regulatory mechanisms of adrenocortical steroid synthesis, secretion, degradation, and/or recycling, at the level of the zonae glomerulosa (aldosterone), fasciculata (GC and GC metabolites), and reticularis (androgens and androgen precursors DHEA and DHEAS). As a whole, these adrenocortical perturbations contribute to the development of metabolic syndrome at both the paracrine and systemic level by favoring the physiological dysregulation of organs responsive to aldosterone, GC, and/or androgens, including adipose tissue.

adrenal gland; adipocytes; angiotensin II; adrenocorticotropic hormone; adrenal steroids

INSULIN RESISTANCE (IR), which is characterized by an insufficiency in insulin action, is associated with pathologies related to the metabolic syndrome, such as central obesity, hypertension, and dyslipidemia, and leads to increased risk of type 2 diabetes and cardiovascular diseases. Common forms of obesity and type 2 diabetes are polygenic diseases, resulting from complex interactions between genetic predispositions and environmental factors (18, 42), with particular importance of dietary fat intake (114, 146). Current data converge to indicate that dysregulation in adipose tissue physiology is one of the primary events in the development of insulin resistance (52, 109, 111), although other insulin- and glucocorticoid-responsive organs such as skeletal muscles and liver may also play a primary role (144, 168). Several publications and reviews also point to glucocorticoids (GC) (151, 190) and the renin-angiotensin system (RAS) as key players in controlling adipose tissue physiology (187). However, several reports indicate cross-talk relationships among the hypothalamo-pituitary-adrenal (HPA) axis, the melanocortin pathways, and the adipose tissue. Combination of certain gene variants with environmental factors, such as overheating, sedentarity, and chronic stress, appears to alter this cross talk, hence inducing perturbations in the regulatory mechanisms of adrenocortical steroid synthesis, secretion, degradation, and/or recycling. The aim of the present review is to explore the dysregulation of adrenocortical secretions as a major contributor in the development of obesity and insulin resistance.

Structure and Functions of the Adrenal Cortex

The adrenal cortex synthesizes and secretes steroids, while the medulla produces catecholamines and several neuropeptides (53, 64). The zona glomerulosa is specialized in the production of aldosterone, whereas the zona fasciculata and zona reticularis synthesize GC (corticosterone in rodents and cortisol in humans, bovine, and hamster). In humans and higher primates, the zona reticularis, and to a lesser extent the zona fasciculata, produce C19 androgens, including large amounts of the precursors DHEA (dehydroepiandrosterone) and DHEA-sulfate (DHEAS) (153) (Fig. 1). The overall production of aldosterone is in picomolar range compared with the micromolar range for cortisol/corticosterone (152). GC and C19 steroids secretion are mainly controlled by the adrenocorticotropic hormone (ACTH), whereas aldosterone secretion is mainly regulated by angiotensin II (ANG II). However, in physiological conditions, all adrenal steroids may also be regulated by a complex interaction of several systemic or paracrine factors. These factors include cells in the vascular wall and immune system, as well as local growth factors and/or neuropeptides from the medulla (64).
As summarized in Fig. 1, aldosterone stimulates sodium reabsorption, hence sustaining blood volume and pressure in the face of salt deprivation or extracellular excretion of potassium, as well as protecting extracellular fluid from excessive levels of sodium (73). Excessive aldosterone secretion leads to hypertension and electrolyte imbalance. Aldosterone and other mineralocorticoids in excess also exert progressive and direct effects in the heart, kidneys, and vessels, leading to hypertrophy, fibrosis, and dysfunction, thereby contributing to degenerative cardiovascular diseases (200). Aldosterone excess is also associated with glucometabolic alterations and IR in the cardiovascular system (76, 77). GC play an important role in the regulation of metabolic homeostasis, initiating a broad range of actions on various organs (162). For example, acute GC secretion during stress mobilizes peripheral amino acids from muscle as well as fatty acids and glycerol from peripheral fat stores to provide substrates for glucose synthesis by the liver. However, chronically elevated GC levels alter body fat distribution and increase visceral adiposity as well as metabolic abnormalities in a fashion reminiscent of metabolic syndrome (23, 24). At the cellular level, GC may reduce insulin signaling via stimulation of oxygen species production and oxidative stress (88). Gonads are the exclusive sources of testosterone in almost all mammals. However, in humans, the adrenal cortex produces small amounts of testosterone and, above all, large amounts of precursors DHEA and DHEAS, which are converted to testosterone in peripheral target tissues. Indeed, in men with normal gonadal function, testes produce 90–95% of circulating testosterone, which corresponds only to ~50% of the total amount of androgen (105). In women, adrenal gland contribution to androgen production is even more important. Indeed, ovaries produce only 25–30% of circulating testosterone in women of reproductive age (147), whereas adrenal glands are virtually the exclusive source of circulating testosterone in postmenopausal women (45). Excessive adrenal androgenic function is linked to the development of polycystic ovary syndrome (PCOS) (14). This common endocrine disorder, also characterized by menstrual disturbances and infertility, exhibits a strong association with metabolic syndrome (16, 46, 141).

The adrenal gland has the ability to adapt its morphology according to physiological conditions. Indeed, prolonged low-sodium diet increases the width of the zona glomerulosa, an effect mainly associated with ANG II action (124), while ACTH treatment increases the volume and blood flow of the zona fasciculata (122). An association between enlarged adrenal glands and type 2 diabetes has been reported in obese patients (78). Adrenal gland weight is also higher in rats fed a high-fat diet (148). On the other hand, patients with classical congenital adrenal hyperplasia (CAH) have an increased inci-
GC recycling metabolism is mediated by 11β-HSD2. The liver has direct access to the liver through the portal vein (192). Local GC production occurs primarily in visceral adipose tissue and amplitude to the original adrenal cortisol production. This local magnitude of this local GC recycling may be of similar lar/cellular concentration of cortisol in adipose tissues (158). Generally have normal or subnormal plasma cortisol concentra-

tion in an autocrine/paracrine fashion. Local GC metabolism is also modulated by steroid 5α- and 5β-reductases (Fig. 1). These enzymes, also expressed in the adrenal gland, convert GC into inactive metabolites. GC metabolism by these steroid reductases is increased in human obesity (6) and in obese (homozygous jaf/jaf) Zucker rats (113). Indeed, adrenal gland weight is higher in rats fed a high-fat diet, which may reflect increased HPA axis activity (148). Although initially presumed to be inactive, 5α-metabolites of GC are now known to bind and activate the GC receptors (125), which are also expressed in the adrenal cortex (142).

Together, these observations indicate that, even if obese patients generally have normal or subnormal plasma cortisol concentrations (131, 158), triglyceride accumulation in visceral adipose tissue may be due, at least in part, to the local production of GC in insulin- and GC-responsive organs such as adipose tissue, liver, and skeletal muscle. In addition, the adrenal gland may be able to modulate overall local and systemic GC metabolism via autocrine, paracrine, and systemic influences and may be in a hyperactive state without apparent increase in plasma cortisol/corticoestrogen levels.

**Role of GC excess in abdominal obesity.** GC play key roles in the regulation of glucose, fatty acid, and amino acid metabolism, in energy partitioning, and in body fat partitioning (191). In adipocytes, cortisol inhibits lipid mobilization in the presence of insulin, thus leading to triglyceride accumulation and retention. Since the density of GC receptors is higher in intra-abdominal (visceral) fat than in other fat depots, the activity of cortisol leading to accumulation of fat is accentuated in visceral adipose tissue (24, 158), providing a mechanism by which excessive endogenous or exogenous GC lead to abdominal obesity and IR (151). However, although metabolic syndrome (visceral obesity, insulin resistance, type 2 diabetes, and dyslipidemia) may in fact resemble Cushing's syndrome (characterized by excessive cortisol secretion), obese patients generally have normal or subnormal plasma cortisol concentrations (131). This may be explained by an increased intratissular/cellular concentration of cortisol in adipose tissues (158).

Intracellular GC may be produced from recycling of GC metabolites such as cortisone in adipose tissues (163). The magnitude of this local GC recycling may be of similar amplitude to the original adrenal cortisol production. This local GC production occurs primarily in visceral adipose tissue and has direct access to the liver through the portal vein (192). Local GC recycling metabolism is mediated by 11β-hydroxysteroid dehydrogenase enzymes (11β-HSD1 and 11β-HSD2). 11β-HSD1 is expressed mostly in insulin target tissues (such as liver, adipose tissue, and brain) and is able, in vivo, to resynthesize cortisol from cortisone, whereas 11β-HSD2, which is expressed mainly in aldosterone-target tissues (such as the kidney), converts cortisol to cortisone (151). Cortisol also increases 11β-HSD1 expression in human adipocytes (33). Studies on selective pharmacological inhibition of 11β-HSD1 performed in rodents have indicated an important role for elevated visceral adipose tissue expression of 11β-HSD1 and local production of GC in the development of IR (175, 191, 192). In humans, elevated 11β-HSD1 expression in visceral adipose tissue is also associated with obesity (54, 126). Local GC production and increased GC receptor (GR) level, associated with the metabolic syndrome, have also been reported in liver (129) and in skeletal muscle (195).

11β-HSD1 and 11β-HSD2 are both expressed in the human adrenal cortex (Fig. 1). They are respectively up- and down-regulated in aldosterone-secreting and in cortisol-secreting adrenal adenomas (4, 123) and may thus regulate GC production in an autocrine/paracrine fashion. Local GC metabolism is also modulated by steroid 5α- and 5β-reductases (Fig. 1). These enzymes, also expressed in the adrenal gland, convert GC into inactive metabolites. GC metabolism by these steroid reductases is increased in human obesity (6) and in obese (homozygous jaf/jaf) Zucker rats (113). Indeed, adrenal gland weight is higher in rats fed a high-fat diet, which may reflect increased HPA axis activity (148). Although initially presumed to be inactive, 5α-metabolites of GC are now known to bind and activate the GC receptors (125), which are also expressed in the adrenal cortex (142).

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**Stress-induced excess in GC is associated with increased food intake.** Adrenal GC and C19 androgen steroid secretion are mainly controlled by pituitary ACTH. ACTH is produced from the larger precursor proopiomelanocortin (POMC), which is also the precursor of the melanocortins 5α-, 5β- and γ-MSH (melanocyte-stimulating hormones) (43). ACTH, through its own receptor MC2R (melanocortin 2 receptor), plays a pivotal role in homeostasis, metabolism, and stress response, all of which are related to its capacity to stimulate the adrenal cortex. In response to various sensorial stimuli during feeding, corticotropic-releasing hormone (CRH) is released from the hypothalamus where it binds to its receptors in the anterior pituitary, thus inducing ACTH secretion. ANG II also participates in the stress response (9, 93), increasing the expression of CRH in the paraventricular nucleus (PVN) in the hypothalamus (2, 10, 92). HPA axis activity and acute stress response are controlled by a feedback inhibitory loop, exerted by GC receptors located in hippocampus, prefrontal cortex, and hypothalamus regions of the brain. This feedback ensures the return to a basal state of secretion (103), as following an acute stress response (Fig. 2).

Acute stress, characterized by an important but transient increase in GC, induces fatty acid mobilization and decreased food intake; moderate but sustained chronic stress, on the other hand, is associated with chronic cortisol secretion and central obesity as well as endocrine, metabolic, and hemodynamic abnormalities (23, 24, 103, 157). Indeed, chronically elevated GC levels redistribute fat from subcutaneous depots to visceral adipose tissue (48), abdominal obesity being a critical feature of metabolic syndrome (55). This fat accumulation and redistribution is further potentiated by the increase in insulin level secondary to GC-induced insulin resistance, mainly at the liver (48) and skeletal muscle level (5). GC also appear to increase the lipolytic response of visceral adipose tissue to stress (11).

Several reports indicate that chronic GC excess is also able to increase food intake (“stress eating”) (23, 48, 49). Central regulation of food intake involves various cross talks between...
In response to various stimuli (from senses, feeding, acute stress), corticotropin-releasing hormone (CRH) is released from the paraventricular nucleus (PVN) of the hypothalamus, where it binds to its receptors at the anterior pituitary, thus inducing adrenocorticotropic hormone (ACTH) secretion. Hypothalamo-pituitary-adrenal (HPA) axis activity is controlled by a feedback inhibitory loop exerted by GC receptors (GR), located mainly in the hippocampus region of the brain. Regulation of food intake involves various cross talks between central orexigenic neuropeptide Y (NPY) and anorexigenic melanocortin peptides (α-MSH) and the peripheral hormones leptin and insulin. Leptin is secreted by fat cells in proportion to body fat stores. Leptin and insulin inhibit arcuate nucleus (ARC) gene expression and secretion of NPY while stimulating proopiomelanocortin (POMC) gene expression in the ARC. In the brain, α-MSH, through binding to melanocortin 4 receptor (MC4R), plays a direct role in the central regulation of eating. Leptin also inhibits expression of the agouti-related peptide (AGRP), the MC4R, and MC3R antagonist. In excess, GC enhance NPY content in the ARC and induce leptin secretion and leptin resistance, thus blunting leptin-induced reduction of food intake and therefore increasing the intake of food. In addition, sleep perturbations stimulate the HPA axis by inducing POMC expression, thus increasing ACTH and GC secretion. There is evidence suggesting that GC secretion is also influenced by the same neuropeptides (CRH, POMC/ACTH, NPY), originating from the adrenal medulla. The melanocortin and leptin pathways may act directly at the adrenal gland level, since MC4R, MC3R, AGRP, and ObRs are all expressed in the adrenal cortex. In particular, AGRP exerts an inhibitory paracrine role on ACTH-induced cortisol production by antagonistic action on MC4R.

During chronic stress, adrenal steroid secretion can also be regulated by modulatory systems that may be independent of the HPA axis. Among these are hormones and receptors implicated in the regulation of food intake, which are all expressed in the adrenal gland. For example, NPY, which is colocalized with catecholamines in postganglionic sympathetic fibers and in the adrenal medulla, plays a role in the regulation of both aldosterone and corticosterone secretion (170, 194). Leptin from the adjacent or intra-adrenal adipose tissue (65) also acts directly at the adrenal gland level by inhibiting its growth and GC secretion (150, 193). Both MC3R and MC4R are expressed in rat adrenal gland and can bind ACTH with the same affinity as α-MSH (58, 177). MC4R is also expressed in human adrenal tissue, whereas MC3R expression has been detected in the human adrenocortical cell line H295R (60). AGRP is present in bovine adrenocortical cells and inhibits both acute and long-term Nle4,D-Phe7 (NDP)-α-MSH- and ACTH-induced cortisol production by antagonistic action toward MC4R, in addition to inhibiting ACTH-induced long-term cortisol production, in a biphasic manner independent of MC2R (59–61). Adrenal AGRP is also upregulated in patients with Cushing’s syndrome in accordance with an inhibitory paracrine role in the human adrenal gland (57) (Fig. 2).

Together, these data indicate that several modulatory systems, at both the central and peripheral level and from either central orexigenic [neuropeptide Y (NPY)] and anorexigenic (melanocortins, mainly α-MSH) peptides and the peripheral hormones leptin and insulin. In the brain, α-MSH plays a major role in the central regulation of eating behavior, directly through binding to MC4R (melanocortin 4 receptor), as well as indirectly through its binding to MC3R (melanocortin 3 receptor), which controls fat storage in adipose tissue and energy expenditure (103, 164). AGRP (agouti-related peptide), a potent and specific antagonist of MC3R and MC4R (137), is upregulated in obese and diabetic mouse models (85) and in obese men (95).

Leptin is secreted by adipocytes in proportion to body fat stores (72) and its primary effect is to inform the brain on the abundance of body fat (3, 70). Leptin inhibits the orexigenic NPY expression and secretion while stimulating POMC expression in the arcuate nucleus (ARC) (13). Leptin exerts opposite actions on AGRP and POMC expression by controlling opposite patterns of their promoters coactivator- corepressor, thus resulting in repression of AGRP and upregulation of POMC (98) (Fig. 2). During prolonged stress, GC in excess enhance the NPY content in the ARC and induce leptin secretion as well as leptin resistance, thus blunting leptin-induced reduction of food intake (13). Administration of large doses of GC thus induces overeating, resulting in obesity despite elevated leptin levels (203).
ANG II is the end product of the RAS. Upon stimulation by either endocrine or paracrine sources, interact to control GC production by the adrenal gland. They also indicate that the response to stress may be completely different according to the nature of the stress. Indeed, chronic stress-induced increase in GC favors food intake and visceral fat accumulation thus facilitating the emergence of metabolic syndrome.

**Correlation between sleep disturbance and dysregulation of the HPA axis.** During the past few decades, sleep curtailment has become a very common annoyance in industrialized countries. This trend toward shorter sleep times has occurred over the same time period as the dramatic increases in the prevalence of obesity and diabetes. Current evidence suggests a close relationship among endocrine, metabolic, cardiovascular, and immune functions and sleep disturbances (149, 183). In studies of healthy young adults subjected to recurrent partial sleep restriction, increased hunger and appetite leading to overeating and weight gain were observed and were correlated with a decrease in glucose tolerance and insulin sensitivity as well as a decrease in circulating levels of the anorexigenic hormone leptin and a concomitant increase in levels of the orexigenic hormone ghrelin (169, 183).

On the other hand, chronic loss of sleep or perturbation in periodicity is correlated with a disturbance in circadian cortisol rhythmicity and sleep-related growth hormone secretion, both of which are associated with abnormal temporal patterns of glucose tolerance with long-term consequence on the development of obesity (184). Moreover, selective paradoxical (rapid eye movement) sleep deprivation (PSD) is sufficient to cause HPA axis hyperactivation. In rats, PSD increases POMC expression in the hypothalamus and increases ACTH and corticosterone secretion as well as relative adrenal weight (174). PSD also increases steroid 5α-reductase expression in the rat adrenal gland (128), which may increase local GC turnover and potent androgen production. Thus, chronic stress and sleep disturbance are both associated with hyperactivity of the adrenal gland, the result being increased GC secretion inducing food intake and weight increase, which in turn lead to insulin and leptin resistance.

**RAS and Aldosterone in the Development of IR**

Adipose tissue is no longer regarded as a passive energy storage depot but rather as a highly active endocrine gland that produces and secretes a wide variety of hormones, cytokines, and growth factors (69, 72). Some of these adipose secreted products are regulated by components of RAS such as ANG II or by aldosterone. Furthermore, adipocytes and adrenal cortex exhibit cross-talk relationships implicated in the manifestations of IR.

**Role of ANG II in aldosterone secretion and adipocyte physiology.** ANG II is the end product of the RAS. Upon stimulation, renin released in circulation from the kidney cleaves liver-generated angiotensinogen (AGT) to produce an inactive peptide, ANG I, that is further cleaved by angiotensin-converting enzyme (ACE) into the biologically active peptide ANG II. In vivo, ANG II is considered to be the main hormonal stimulus of the zona glomerulosa of the adrenal cortex (132), acting on both aldosterone secretion and zona glomerulosa morphology (138). ANG II also stimulates cortisol secretion in bovine, hamster, and human adrenal glands (36). Most of the actions of ANG II are related to stimulation of growth and regulation of aldosterone secretion and of vascular tone and are mediated through binding to the AT1 receptor subtype (AT1R) (90, 160). Conversely, ANG II stimulation of the ANG II type 2 receptor (AT2R) promotes vasodilatation, growth inhibition, cell differentiation, and apoptosis via complex signaling mechanisms (77, 166, 196). Thus, it is generally assumed that AT2R counteracts the effects of AT1R. Although AT1R is largely expressed, AT2R expression is generally restricted to a few tissues in adults and is found at low levels, but it is highly expressed during cell differentiation, such as adipose differentiation (50, 120). Under certain pathological conditions (heart and renal failure, myocardial infarction, brain lesions, vascular injury, and wound healing), the AT2R has been shown to be upregulated. This suggests a key role for ANG II and AT2R as a beneficial vasodilator and antigrowth signal, thus contributing to the efficacy and therapeutic effects of AT1R antagonists (38, 89, 135, 188, 196) (Fig. 3).

In addition to the systemic RAS, there is also a local RAS in many tissues, including the adipose tissue, which acts in an autocrine/paracrine manner (77). ANG II may thus be involved in the control of adipose tissue physiology since AT1R and AT2R are both expressed in adipocytes. In human adipocytes, for example, AT1R mediates ANG II-induced production of leptin, a marker of adiposity (167). ANG II is also involved in the regulation of adipose tissue blood flow (84, 181). However, in humans, the inhibiting effect of ANG II on adipose tissue blood flow appears to be sex specific, being minimal in healthy men (30). Moreover, the effect of ANG II on adipose tissue lipolysis appears to be species specific. In rats, ANG II stimulates lipolysis in subcutaneous and visceral adipocytes in an AT1R- and a β-adrenergic receptor-dependent manner (34). In normal and obese humans, ANG II rather inhibits adipose tissue lipolysis, also in an AT1R-dependent manner (83, 84). AGT itself may play a role in local adipose tissue blood flow and, hence, in rates of fatty acid reesterification (72, 185).

**Involvement of ANG II and aldosterone in the development of IR.** Various clinical studies have documented elevated plasma aldosterone levels in obese patients, especially those with visceral obesity (80, 82, 106, 171, 179). The fact that blockade of aldosterone action by aldosterone antagonists significantly attenuates the rise in arterial pressure in diet-induced obesity in dogs supports the importance of this hormone in the development of obesity-related hypertension (51). Furthermore, aldosterone in excess may impair insulin release and reduce insulin sensitivity (44). In vitro, aldosterone decreases insulin binding and insulin receptor expression via downregulation of its own receptor, the mineralocorticoid receptor (MR) (35), a receptor that also shows a high affinity for GC (12). Interestingly, aldosterone has been recently reported to promote adipogenesis via activation of MR. Since the inhibition of adipogenesis obtained by siRNA-induced MR downregulation is not mimicked by specific GR inactivation, MR may thus act as a proadipogenic transcription factor mediating the effects of both aldosterone and GC (37).

Various studies also support the involvement of ANG II in the development of IR and type 2 diabetes (77, 160). Indeed, in obesity as in type 2 diabetes, many elements of the RAS cascade are upregulated, such as renin, AGT, and ANG II as well as AT1R and AT2R (77). This activation of local RAS plays a key role in end-organ damage induced by type 2
diabetes. Much of the deleterious effects of ANG II (oxidative stress, inflammatory, proteolytic, and fibrotic processes) are mediated by AT1R, hence explaining the therapeutic effects of ACE inhibitors and AT1R blockers on diabetic nephropathy and cardiovascular complications (1, 77). Indeed, AT1R blockade abolishes the ANG II-induced expression of several adipocytokines in mouse mature adipocytes (100). AT1R blockers also decrease plasma triglycerides and nonesterified fatty acid levels in fructose-fed rats (136) and in obese Zucker rats (154), thus increasing free fatty acid (FFA) uptake by adipocytes and reducing inflammatory activation as well as production of reactive oxygen species (ROS). Further details on this signaling can be found in Schiffrin et al. (160).

In the cardiovascular system, stimulation of AT2R primarily induces activation of phosphotyrosine phosphatases and caspase 3, with a decrease in p42/p44MAPK activity. On the other hand, peroxisome proliferator-activated receptor-γ (PPARγ) is involved in vasoprotection and anti-inflammatory responses. Among the stimuli of PPARγ are some specific antagonists of AT1R. As illustrated, most of the effects mediated by the AT1R are related to vasoconstriction and cell growth, whereas the effects of the AT2R, either alone or together with PPARγ, have a protective action against the deleterious effects mediated by the AT1R. TZDs, thiazolidinediones.

Fig. 3. Main cellular pathways and biological actions associated with the ANG II receptor subtypes (AT1R and AT2R). ANG II is produced from the conversion of angiotensinogen in ANG I by renin (released in circulation from kidney). ANG I is further cleaved by angiotensin-converting enzyme (ACE) to the biologically active peptide ANG II. Stimulation of AT1R by ANG II activates several signaling pathways, including phospholipase C-induced phosphatidylinositol breakdown, the MAP kinase pathways, p42/p44MAPK and the p38 MAPK, and generation of reactive oxygen species (ROS). Further details on this signaling can be found in Schiffrin et al. (160). In the cardiovascular system, stimulation of AT2R primarily induces activation of phosphotyrosine phosphatases and caspase 3, with a decrease in p42/p44MAPK activity. On the other hand, peroxisome proliferator-activated receptor-γ (PPARγ) is involved in vasoprotection and anti-inflammatory responses. Among the stimuli of PPARγ are some specific antagonists of AT1R. As illustrated, most of the effects mediated by the AT1R are related to vasoconstriction and cell growth, whereas the effects of the AT2R, either alone or together with PPARγ, have a protective action against the deleterious effects mediated by the AT1R. TZDs, thiazolidinediones.

Activation of AT2R mediates the ANG II-induced increase in expression of adiponectin, an insulin-sensitizing hormone secreted by adipose tissue (41), whereas AT1R mediates a decrease in plasma adiponectin levels (155) (Fig. 3). Moreover, chronic infusion of ANG II robustly stimulates AT1R type A (AT1βR) and AGT expression in mice adipose tissue. In AT2R-deficient mice, this ANG II effect is higher, and AT1R blockade abolishes the increased expression of adipose AGT (115). These observations are consistent with the observations that actions mediated by AT2R are opposite to those triggered by AT1R and that activation of AT2R is known to mediate potential beneficial effects on adipose tissue function. However, the respective roles of AT1R and AT2R in adipose tissue physiology are not so simple. AT1βR-deficient mice exhibit attenuation of diet-induced weight gain and adiposity (100) as expected. AT2R-deficient mice, however, are surprisingly protected from diet-induced obesity and insulin resistance, albeit displaying an increased number of smaller sized adipocytes (201). Moreover, adipose tissue depletion during food deprivation is also prevented in these AT2R-deficient mice (202). The balance between lipid storage in adipose tissue and lipid utilization by organs and muscles may thus require equilibrium between AT1R and AT2R in adult tissues where AT2R expression remains at a relatively high.
level, such as the adrenal cortex (71, 107), the adipose tissue (161), and the pancreas (39).

**Relationship between ANG receptors and peroxisome proliferator-activated receptor-γ.** Peroxisome proliferator-activated receptors (PPARα, -γ, and -δ) are members of the nuclear receptor family and play a key role in the regulation of adipocyte differentiation, insulin sensitivity, glucose and lipid metabolism, and inflammation (21, 25, 56). PPARs are activated, to varying degrees, by fatty acids, including certain forms of oxidized linoleic acid and by PPARγ pharmacological agonists (180). PPARγ, which displays a restricted expression pattern, is abundantly expressed in adipose tissue and in the adrenal gland (99). Indeed, PPARγ pharmacological agonists, such as thiazolidinediones (TZDs) are known to inhibit growth and androgen production in the human ANG II-responsive adrenocortical cancer cell line H295R (68, 96). In the human ACTH-responsive NCI h295 adrenocortical cancer cell line, TZDs decrease proliferation and viability but increase ACTH receptor (MC2R) expression, cortisol secretion, and apoptosis (22). In PCOS patients, where insulin appears to directly enhance adrenal steroidogenesis, TZDs reduce adrenal androgen response to CRH (156). The cross talk between PPARγ and GC appears to be bidirectional and also occurs at the local level, as 11β-HSD1-deficient mice, hence deficient in local GC regeneration, exhibit higher expression of adipose PPARγ (130).

Some specific AT₁R blockers are capable of binding and activating PPARγ (143) and are now considered as selective PPARγ modulators that behave as partial PPARγ agonists (205). In rodents, these specific AT₁R blockers improve diet-induced obesity, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia (8, 20). In addition, they repress AT₁R expression via PPARγ (91), whereas PPARγ agonists such as TZDs markedly increase insulin sensitivity and adiponectin expression and improve ANG II-induced vascular remodeling (180) through interference with the AT₁R signaling pathway (19). The beneficial metabolic effects of specific AT₁R blockers may require an intact leptin-signaling system, since they have little impact on obese Zucker rats that harbor mutant leptin receptors (20). In addition, since AT₁R and AT₂R often appear mutually antagonistic, AT₂R activation may mediate, at least in part, some effects of AT₁R blockade, including those on PPARγ (97) (Fig. 3). Indeed, treatment with AT₁R blocker increases the expression of adiponectin and PPARγ as well as AT₂R expression in adipose tissue (207), whereas AT₂R mediates the ANG II-induced increase in adiponectin (41) and PPARγ expression and transactivation activity (206). The above-mentioned observations reinforce the hypothesis that the positive effects of AT₁R blockade in metabolic syndrome may be due, at least in part, to AT₂R activation (38, 89, 135, 188, 196) and subsequent PPARγ activation (207).

**Cross talk between adrenal gland and adipose tissue.** There is some evidence suggesting the existence of a cross-talk relationship between adipose tissue and the adrenal gland. The Ehrhart-Bornstein group (65) has shown that adipocytes produce mineralocorticoid-releasing factors that can reach the adrenal gland in sufficient concentrations to stimulate aldosterone secretion. Indeed, the adrenal glands are embedded in adipose tissue. On the other hand, adipocytes have frequently been observed in proximity to adrenal vessels or as clusters in zona glomerulosa and fasciculata, where they are in direct contact with steroid-producing cells. This adipocyte aldosterone-releasing activity is not associated with ANG II, since it is not inhibited by candesartan (an AT₁R blocker) in a rat model of metabolic syndrome and is not observed in adipocytes from nonobese spontaneously hypertensive (SHR) rats (133). However, identification and further characterization of these factors remain to be explored.

Obesity-associated increase in oxidative stress and elevated plasma FFA levels may activate the HPA axis, thus increasing ACTH and corticosterone levels (197). In fact, unsaturated fatty acids directly stimulate adrenal GC and aldosterone production in the absence of ACTH (81, 159). Studies have indeed shown that EKODE, an oxidized derivative of the polyunsaturated fatty acid linoleic acid, increases both basal, ACTH-induced corticosterone and ANG II-induced aldosterone production in rat adrenocortical cells (31), possibly explaining the relatively high levels of aldosterone in some subjects with visceral obesity (80, 82). Indeed, plasma EKODE level correlates directly with aldosterone level, body mass index, and systolic pressure in an African American cohort (81). Together, these results indicate that unidentified factors secreted by adipocytes or even FFA excess (oxidized or not) can modulate adrenal steroid secretion independently of ANG II or ACTH, further revealing a close interaction between adipose tissue and adrenal gland physiology (Fig. 4).

**Androgens, PCOS, and IR**

PCOS, a common endocrine disorder affecting 5–10% of women of reproductive age (101), displays a strong association with metabolic syndrome (type 2 diabetes, obesity, cardiovascular diseases) (16, 46, 141). It is already known that hyperandrogenism, the main clinical feature of PCOS (14), correlates positively with hyperinsulinemia (15, 17, 63) and that adrenal gland androgens contribute to PCOS (127, 199). In women, a rare 11β-HSD1 polymorphism leading to lower 11β-HSD1 activity is associated with enhanced cortisol clearance and reduced negative feedback suppression of ACTH secretion. This results in an increase in adrenal cortisol production to maintain plasma cortisol levels, which ultimately leads to compensatory adrenal hyperandrogenism and a phenotype resembling PCOS (62, 145). Recently, this 11β-HSD1 polymorphism was correlated positively with lean PCOS status: the reduced cortisol regeneration capacity observed in these lean PCOS women may thus constitute a protective mechanism against metabolic syndrome (75).

In PCOS, it is well known that altered cortisol clearance is associated with enhanced steroid 5α-reductase activity (172) and that insulin likely increases the 5α-reduction of steroids (182). Thus 11β-HSD1/11β-HSD2 enzymes are not the only enzymatic system having a major role in local GC metabolism in adipose tissue. Moreover, although presumed to be inactive, 5α-metabolites of GC (but not the 5β-metabolites) are now known to be able to bind and activate the GR (125). The preferential expression of GR in the zona reticularis of the adrenal cortex suggests a role of GC in adrenal androgen biosynthesis (142). The types 1 and 2 steroid-5α-reductases (SRD5A1 and SRD5A2) are also involved in the conversion of adrenal precursors and testosterone into 5α-dihydrotestosterone (DHT), the most potent natural androgen, and may thus be involved in increased production of androgens observed in...
PCOS (67) (Fig. 1). Steroid 5α-reductases are expressed in many tissues, including the adrenal gland in rodents (in zonae fasciculata and reticularis for SRD5A1) (116). Steroid 5α-reductase activity is regulated not only by sex hormones (110), but also by GC (119) and even by sleep deprivation (128). Some polymorphisms in steroid 5α-reductase genes have been recently associated with PCOS (79).

In human cultured adrenocortical cells, the oxidized fatty acid EKODE has no effect on basal cortisol production but decreases ACTH-induced cortisol production while stimulating basal and ACTH-induced DHEA production (32). In men, FFA are known to increase the production of adrenal androgen precursors (DHEA and androstenedione) in vivo (118). Prolonged experimental elevation of plasma FFA in vivo has also been shown to reduce muscle and hepatic glucose insulin sensitivity in humans (111). Plasma FFA levels are increased in obese PCOS women (vs. controls) and are correlated with resistance to insulin-stimulated glucose metabolism (87). Therefore, increased expo-
anandamide, an endogenous CB1 ligand, associated with a low tissue accumulation. The adrenal gland displays the highest accumulation of anandamide (198), which suggests that the adrenal gland may be a major target organ for pharmacological CB1 antagonists.

**Conclusion**

The evidence outlined in the present review indicates that perturbations in adrenocortical steroidogenesis have an important impact on food intake, glucose metabolism, lipid storage, and energy balance: 1) chronic stress-induced GC excess is associated with increased food intake and abdominal/visceral obesity; 2) the increase in aldosterone also favors adipogenesis and is responsible for hypertension along with concomitant risks of developing atherosclerosis and cardiovascular diseases; 3) GC enhance 11β-HSD1 expression, thereby presumably amplifying local GC production, notably in visceral adipose tissue; 4) the overall increase in GC (systemic and/or local) leads to insulin resistance, mainly at the adipose tissue, liver, and skeletal muscle level; 5) aldosterone and the overall increase in GC are associated with hyperactivity of the RAS, notably at the adipose tissue level, which further stimulates GC and aldosterone production. When initiated, these perturbations thus induce a feed-forward loop that contributes to maintaining all of these systems in activated mode such as an endless spiral: more GC in the systemic and/or local level leads to more GC at the adipocyte level, which leads to more insulin resistance, more aldosterone, and more local production of ANG II, etc. In humans, perturbations of local androgen production and metabolism, which are supplied in part by adrenal precursors, also appear to be involved in a sex-dependent fashion. Thus, dysregulation of adrenocortical steroidogenic activities, in interaction with hyperactivity of the hypothalamo-pituitary complex and of the RAS as well as increased GC reactivation and altered androgen metabolism at local levels, may all be involved in the development of obesity and insulin resistance, henceforth leading to metabolic syndrome-associated pathologies such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases (Fig. 4).

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