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Unsolicited Review

Adrenal–adipose tissue crosstalk in health and disease

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Abstract

Adipose tissue (AT) closely interacts with the adrenal glands to regulate metabolism, energy balance, and stress responses. While the adrenal cortex secretes glucocorticoids and mineralocorticoids that influence AT distribution, lipid storage, and browning, the adrenal medulla releases catecholamines that acutely activate thermogenesis in brown and beige adipocytes. Under physiological conditions, this bidirectional crosstalk maintains energy homeostasis and cardiovascular stability. However, in adrenal diseases such as Cushing syndrome, primary aldosteronism, adrenocortical carcinoma, or pheochromocytoma, excess hormone secretion disrupts this balance, leading to AT dysfunction, altered adipokine secretion, and adverse metabolic profiles, including insulin resistance, visceral adiposity, and hypertension. Emerging evidence suggests that peri-adrenal AT may modulate adrenal tumor biology through endocrine and paracrine signals, and immune cell infiltration, with potential effects on disease progression and clinical presentation. Uncovering cellular and molecular mechanisms underlying the crosstalk between adrenal gland and AT may reveal new therapeutic targets for the reduction of cardiometabolic complications in patients with adrenal disorders. Here, we discuss how 2 endocrine organs—adrenal gland and AT—interact with each other under physiological and pathophysiological conditions and examine whether these interactions influence the progression of adrenal tumors and how this affects systemic metabolic health.

Keywords: steroids, catecholamines, fat browning, Cushing syndrome, paraganglioma, primary aldosteronism, adipokines

Significance

The adrenal gland and adipose tissue interact in a bidirectional crosstalk that is essential for maintaining metabolic and cardiovascular homeostasis. Adrenal hormones play a role in the regulation of adipose tissue distribution, lipid storage, and adipocyte thermogenesis. Conversely, adipose-derived mediators can influence adrenal function and stress responses. Excess hormone secretion disrupts the balance in adrenal disorders such as Cushing syndrome, primary aldosteronism, adrenocortical carcinoma, and pheochromocytoma, promoting adipose dysfunction, insulin resistance, visceral adiposity, and hypertension. Furthermore, emerging evidence suggests that peri-adrenal fat may influence adrenal tumor behavior. A better understanding of the cellular and molecular mechanisms controlling adrenal–adipose interaction could reveal new therapeutic targets to mitigate cardiometabolic complications and improve outcomes in patients with adrenal diseases.

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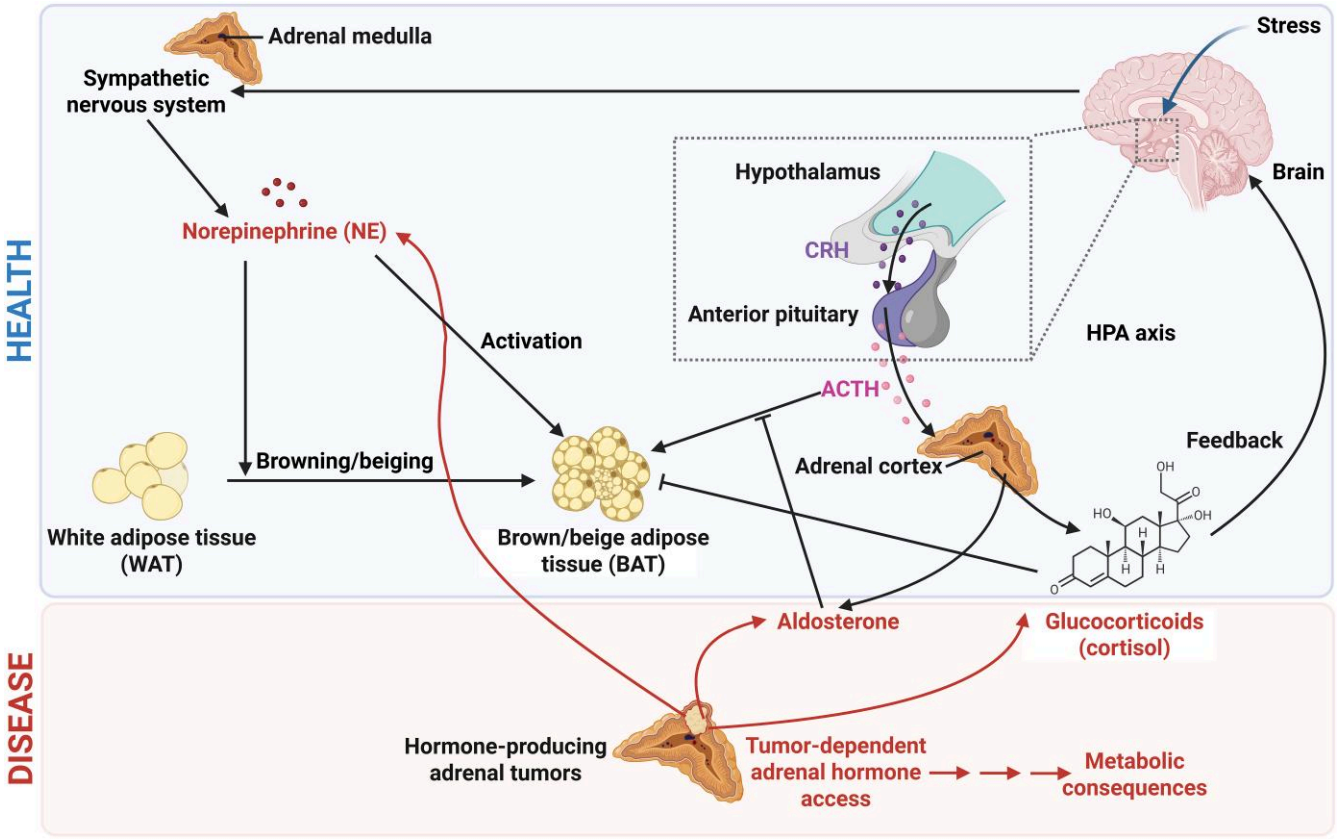
Graphical Abstract



Introduction

The adipose tissue (AT) has been recognized as an active endocrine organ that plays a key role in maintaining homeostasis and is involved in the pathogenesis of different diseases.[1-3] Extensive research has revealed that distinct adipose depots regulate not only energy storage and consumption, but also the secretion of adipokines and signaling molecules that affect local and distant organs. Patients with adrenal tumors show an increased prevalence of metabolic and cardiovascular complications.[4] The adrenal gland comprises the steroid-producing cortex and the catecholamine-producing medulla, both enclosed within a common capsule and surrounded by perirenal AT (peri-AT; Figure 1A). However, potential crosstalk between these endocrine tissues remains poorly understood.

The adrenal gland maintains body homeostasis by producing neuronal, metabolic, and endocrine signals that regulate metabolism, stress response, electrolyte balance, and cardiovascular function. The adrenal cortex comprises 3 zones: the zona glomerulosa (zG) produces mineralocorticoids controlling electrolyte balance and blood pressure, the zona fasciculata (zF) synthesizes glucocorticoids (GC) regulating metabolism and immunity, and the zona reticularis (zR) generates androgens, precursors of sex hormones. The cortex also mediates stress responses via the hypothalamic–pituitary–adrenal (HPA) axis, where internal and external stimuli trigger corticotropin-releasing hormone (CRH) secretion from the hypothalamus. Corticotropin-releasing hormone stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland, resulting in the release of GC by the zF.[5] Furthermore, during acute stress (fight-or-flight response), chromaffin cells of the adrenal medulla secrete catecholamines (epinephrine and norepinephrine (NE)).[6] Since cortex and medulla share a common capsule, changes in one compartment affect the other. Interactions between cortical and chromaffin cells are essential for maintaining adrenal function under physiological and pathophysiological conditions.[7]

Pathophysiological alterations of the adrenal are usually associated with an over- or underproduction of adrenal hormones, leading to local and systemic metabolic changes. Pheochromocytomas are catecholamine-producing tumors with heterogeneous presentations, ranging from dopamine-only to epinephrine- or NE-producing phenotypes or even non-functional tumors.[8] Chronic catecholamine excess associated with these tumors drives a pro-inflammatory and hypermetabolic state, causing weight loss despite normal food intake.[9-11] In contrast, adrenal Cushing syndrome (CS), caused by autonomic cortisol hypersecretion due to an adrenal tumor, results in profound metabolic changes, including insulin resistance, dyslipidemia, and increased visceral adiposity, which contributes to significant weight gain and redistribution.[12,13] The overproduction of aldosterone in patients with primary aldosteronism (PA) has also direct consequences on body fat distribution.[14] For instance, patients with bilateral PA tend to be more obese and have larger visceral fat areas than patients with lateralized PA.[14]

Adrenal tumors frequently cause metabolic and cardiovascular comorbidities through hormone-induced disruption of systemic homeostasis, profoundly affecting AT. Here, we provide novel insights into the bidirectional crosstalk between adrenal, AT, and adrenal tumors, to reveal how these

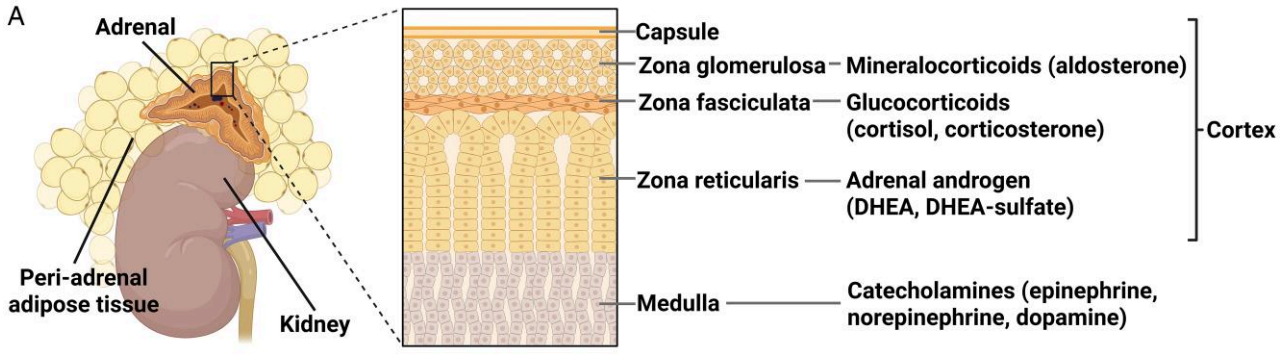
interactions shape tumor biology, local remodeling, and disease manifestations.

Fat depots and fat beigeing/browning

Visceral adipose tissue (VAT) is an independent risk marker for cardiovascular and metabolic morbidity and mortality,[15,16] whereas accumulation of abdominal subcutaneous adipose tissue (SAT) is a much weaker indicator of cardiovascular risk.[16] Emerging evidence also suggests that an accumulation of peri-organ AT is associated with an increased risk for cardiovascular and metabolic disease.[17,18] Adipose tissue accumulation may directly induce organ dysfunction through local mechanisms. For example, peri-vascular AT is involved in the pathogenesis of hypertension.[19] Epicardial AT is associated with atherosclerosis and coronary heart disease,[20] while peri-renal adipose tissue (PRAT) is involved in chronic kidney disease (CKD).[21] This emphasizes the direct influence of AT on adjacent organs.

Previously considered primarily as fat storage depots, adipocytes are now recognized as metabolically active endocrine, autocrine, and paracrine cells that synthesize, store, and secrete hormones and proteins (adipokines). There are 3 major types of adipocytes, which differ in morphology, cellular origin, and physiological function (Figure 1B). White adipocytes are derived from myogenic factor 5 (myf5)-negative progenitors,[22] store energy in the form of triglycerides and secret adipokines.[23] In contrast, brown adipocytes in mice originate from myf5-positive precursor cells and feature multilocular lipid droplets, a round central nucleus and cristae-enriched mitochondria that express uncoupling protein 1 (UCP1).[23] Uncoupling protein 1 is the hallmark of brown adipocytes and promotes energy expenditure. Brown adipocytes are regulated by the sympathetic nervous system and are able to maintain body temperature through thermogenesis. Main depots of human brown adipose tissue (BAT) are located in the supraclavicular and cervical regions, with some additional mediastinal, peri-vertebral, peri-cardial, and peri-renal locations.[24] Beige (or brite or browning of white or inducible) adipocytes resemble brown adipocytes in terms of thermogenic properties[25,26] and are also UCP1-positive, but are unilocular and derived from myf5-negative precursors[25] under specific environmental or hormonal stimuli (eg, cold exposure,[27] β3-adrenergic agonists,[28] and irisin[29]). Brown adipose tissue is found in various depots in humans and can exhibit features of both brown and beige adipocytes. Peri-renal adipose tissue and peri-AT are BAT hot-spots with many brown adipocytes near the adrenals.[30]

Peri-renal adipose tissue is a metabolically active hybrid VAT, which is located in the retroperitoneal space surrounding the kidneys and adrenal glands. Peri-renal adipose tissue exhibited age-dependent molecular and morphological progressive regression, continuously transforming BAT into predominantly white adipose tissue (WAT).[31] In human adult PRAT, dormant unilocular UCP1-expressing adipocytes are widely distributed, whereas active multilocular UCP1-expressing adipocytes are predominantly located around the adrenal, in areas with high numbers of sympathetic nerve endings,[30] which suggests that PRAT and peri-AT are both related and distinct from each other. Peri-renal adipose tissue is more



B

	Function	Secreted factors	UCP1	Mitochondria abundance	Location (human)	Origin
White adipocytes	Energy storage Lipolysis Glucose uptake Adipokine secretion	Leptin Adiponectin Resistin	Negative	Low	Subcutaneous, visceral	Myf5⁻ mesenchymal stem cells
Beige adipocytes	Thermogenesis Catabolism	FGF21 IL-6 SLIT-2	Some negative	High	Supraclavicular, but predominantly in subcutaneous WAT	Myf5⁻ mesenchymal stem cells
Brown adipocytes	Thermogenesis Lipid clearance Catabolism Batokine secretion	FGF21 IL-6 (Batokines)	Positive	High	Anterior cervical, supraclavicular, axillary, paravertebral	Myf5⁺ mesenchymal stem cells

Figure 1 Adrenal and adipocyte function and secretion. (A) Adrenal zonation and hormone production. (B) Function and characteristic features of white, beige and brown adipocytes. Created by BioRender.com.

active than other typical VATs in metabolizing, synthesizing, and secreting adipokines and inflammatory cytokines.[32] A variety of adipokines and cytokines secreted by peri-AT regulate adrenal function and metabolism by local mechanisms.[33-35] Conversely, adrenal hormones affect peri-AT through paracrine and endocrine pathways, which may contribute to tumor-related pathophysiology.[28,36-40]

Adrenal hormones and activation/browning of AT

Brown adipose tissue activity is tightly regulated by adrenal hormones and the sympathetic nervous system (Figure 2). Stress activates the HPA axis, causing cortisol secretion, which suppresses BAT activation and promotes VAT accumulation,[41] while NE released by sympathetic nerves and the adrenal medulla stimulates BAT thermogenesis and white fat beiging via β3-adrenergic receptor activation.[42] Other factors such as cold exposure, ACTH, and fatty acids also enhance browning, whereas insulin inhibits this process. Given the key role of adrenal hormones in AT regulation, their dysregulation profoundly disrupts metabolism and has major clinical consequences. Accordingly, adrenal tumors show hormone-dependent differences in BAT prevalence. While 62.5% of patients with pheochromocytoma (PCC) have brown adipocytes in their retroperitoneal fat mass, this is only the case in ~33.3% of patients with cortisol-producing adenomas and 46.9% of patients with aldosterone-producing adenomas (APAs).[43] The following sections discuss molecular and metabolic mechanisms behind these differences and effects of tumor-related adipose remodeling.

AT–adrenal cortex interactions

Glucocorticoids, mainly cortisol, regulate numerous biological functions in adipocytes, including adipogenesis. GC stimulates differentiation of pre-adipocytes into mature white adipocytes,[44,45] but GC also inhibits development and activation of peri-renal BAT in rodents.[46,47] In humans, GC acutely increases BAT activity but chronically suppresses it, suggesting a time-specific effect of GC on UCP1 and BAT activity.[41,48] This effect is highly species-specific, as GC reduce BAT activity in mice.[48] Moreover, GC inhibit the response of cultured human brown adipocytes to adrenergic stimulation.[49] As an

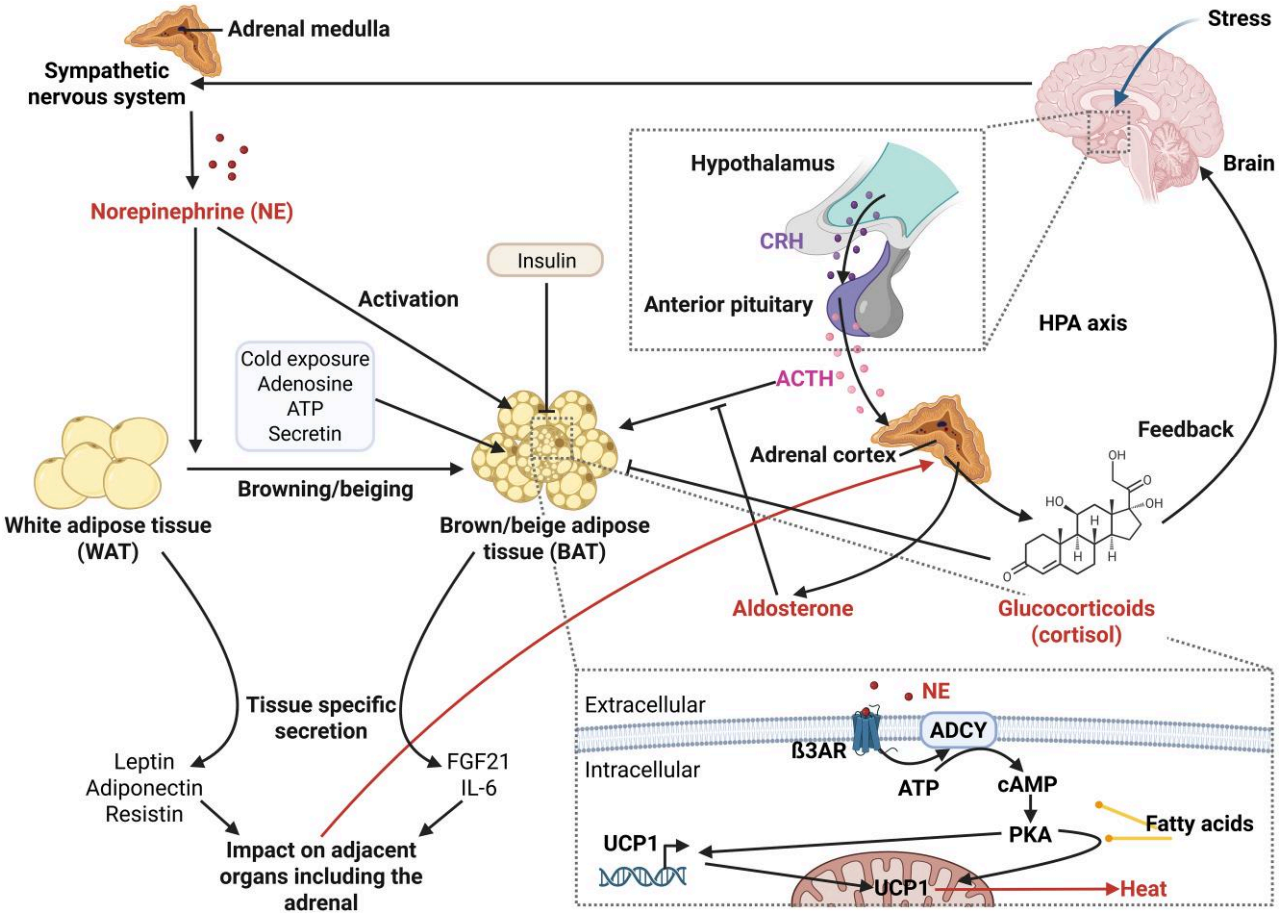


Figure 2 Regulation of brown adipose tissue activity in particular in response to secretion of adrenal hormones. Stress activates the HPA axis. The autonomic nerves system triggers the hypothalamus to release CRH, which induces the release of ACTH in the anterior pituitary. In the adrenal cortex, ACTH leads to the release of cortisol, which suppresses fat browning and increases the accumulation of visceral WAT. In contrast, NE released by the sympathetic nervous system, including the adrenal medulla, causes fat beiging and activation of brown adipocytes. Other factors, such as adenosine, ATP, ACTH, secretin, fatty acids, and other dietary nutrients can contribute to fat browning, while insulin, in addition to cortisol, reduces fat browning. Therefore, NE binds to the beta-3 adrenergic receptor expressed on the surface of adipocytes, which leads to the activation of ADCY, which converts ATP to cAMP. cAMP activates PKA, which causes the expression and activation of UCP1 leading to thermogenesis. Created by BioRender.com. ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; HPA, hypothalamic–pituitary–adrenal; NE, norepinephrine; ATP, adenosine triphosphate; ADCY, adenylate cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; UCP1, uncoupling protein 1.

antagonist, ACTH, which is responsible for the release of cortisol in the adrenal, promotes browning of adipocytes.[50,51]

Intracellular GC activity and metabolism is regulated by 2 isoforms of 11β-hydroxysteroid dehydrogenase (HSD). While type 1 (11β-HSD1) is localized in several tissues, including AT, and converts inactive cortisone to cortisol that binds to the intracellular glucocorticoid receptor (GR), type 2 (11β-HSD2) causes the reverse conversion of cortisol to cortisone, thereby preventing cortisol from occupying the mineralocorticoid receptor (MR) in aldosterone target tissues.[52,53] Under physiological conditions, cortisol is 100-1000 times higher concentrated than aldosterone, and this effect is exacerbated in patients with hypercortisolism.[54,55] Moreover, due to the saturation of 11β-HSD2 enzymatic activity under conditions of cortisol excess, cortisol is even able to bind to MR in aldosterone target tissues.[56] Inflammatory signals, including tumor necrosis factor (TNF) and interleukin (IL)-1β, modulate expression of HSD enzymes, thereby altering cellular sensitivity to GC.[57] The GR, encoded by *NR3C1* (nuclear receptor subfamily 3, group C, member 1), has a much higher affinity for cortisol than aldosterone and is most likely responsible for the inhibitory effects of GC on BAT development and activity.[43,58] However, MR, encoded by *NR3C2* (nuclear receptor subfamily 3, group C, member 2), has a similar affinity for aldosterone and cortisol, and coregulators recruited upon GR and MR binding largely overlap.[59,60] Glucocorticoids play a crucial role in AT metabolism and cause multiple transcriptomic changes and epigenetic modifications.[61-63] Glucocorticoid receptor activation exerts highly tissue-specific effects on the epigenome, which can be controlled by a cell-type-specific binding of GR to target genomic sites[64,65] and can even persist after stimulus is removed. However, studies on the epigenetic regulation of GC or other adrenal hormones in AT are lacking.

Glucocorticoids induce an increased leptin secretion from adipocytes, suggesting a mechanism that may contribute to anorexia and weight loss during stress when these conditions are accompanied by a sustained increase in plasma leptin concentrations.[66] Furthermore, leptin inhibits GC secretion in human adrenocortical cells by the suppression of steroidogenic enzymes,[67] which demonstrates the complex regulation of this system, particularly under stress.

The renin–angiotensin–aldosterone system (RAAS) is a central regulator of blood pressure, fluid, and electrolyte balance, and also affects adipocyte function via MR signaling[68] (Figure 3). Aldosterone prevents ACTH-induced expression of *UCP1*.[47,51,69] Mineralocorticoid receptor is expressed in BAT cells and MR antagonists are able to induce browning of visceral and subcutaneous AT in mice.[70] Mineralocorticoid receptor antagonists can improve BAT function in response to cooling in humans.[71] However, administration of classic steroidal MR antagonists to mice fed a moderately high-fat diet reduces the spread of WAT, induces the activation of interscapular BAT, and stimulates the browning of WAT.[70] The activation of MR also causes adipocyte hypertrophy, which leads to oxidative stress, local hypoxia, and a pro-inflammatory state.[72] In line, MR blockade reduces the expression of pro-inflammatory and prothrombotic factors and enhances adiponectin expression in AT of obese, diabetic mice, revealing a potential mechanism for the cardioprotective effects observed under MR blockade.[73] In vitro, aldosterone appears to be able to induce adipocyte differentiation and intracellular lipid accumulation, suggesting that both MR and GR are vital for adipocyte differentiation.[74,75]

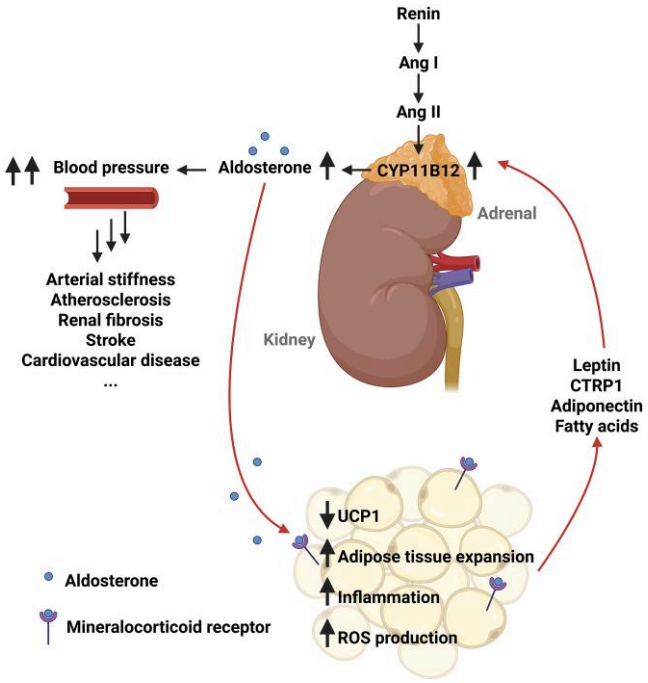


Figure 3 Crosstalk between adipocytes and the RAAS. Created by BioRender.com. RAAS, renin–angiotensin–aldosterone system.

Moreover, adipocytes play a regulatory role in steroidogenesis. Adipocyte-conditioned medium stimulates aldosterone production in adrenocortical cells (NCI-H295R).[76,77] Adipokines, including C1q/TNF-related protein (CTRP1), adiponectin and leptin, can stimulate the production of aldosterone in the adrenal, which links obesity directly with hypertension.[78-80] Leptin directly regulates aldosterone synthase expression in the adrenal and thus aldosterone secretion, contributing to high aldosterone levels observed in obese mice.[81]

Visceral and subcutaneous AT can also produce angiotensinogen and possesses a local renin–angiotensin system.[82] Activation of this local RAAS system in the peri-AT of patients with CS causes high blood pressure levels even 6 months after the remission of hypercortisolism.[33] Adipocyte-derived aldosterone regulates adipocyte differentiation and vascular function providing a potential link between vascular dysfunction in diabetes mellitus–associated obesity.[83]

AT–adrenocortical tumor interactions

Adrenocortical tumors are neoplasms that arise from the adrenal cortex and range from benign adrenal adenomas to highly aggressive adrenal carcinomas. They may be hormonally active and cause clinically significant endocrine syndromes (Table 1), or they may be non-functional and discovered incidentally during imaging examinations.

Cushing syndrome

Adrenal Cushing is caused by autonomous overproduction of cortisol in the adrenal due to benign or malignant adrenal tumors, or due to bilateral primary micro- and macronodular adrenal hyperplasia and accounts for ~20% of all CS cases.[95] Patients with CS typically present with metabolic manifestations such as hyperglycemia, hypertension, and excessive fat deposits in face, neck, and visceral organs.[85,96] The severity

Table 1 Metabolic changes and effects on the peri-AT or peri-renal AT associated with adrenal tumors.

Adrenal disorder	Hormone production	Metabolic changes associated with the disease	Main effects on peri-AT or peri-renal AT	Further key publications
Adrenal medulla				
Pheochromocytoma	Excess catecholamines (epinephrine, norepinephrine)	Hyperglycemia, insulin resistance, weight loss, increased lipolysis[10]	Promotes brown adipose tissue activation and browning phenotype in peri-AT[9,40]	Ref.[9,40,84]
Adrenal cortex				
Cushing syndrome	Excess cortisol	Central obesity, insulin resistance, type 2 diabetes, dyslipidemia[85]	Adipocyte hypertrophy, macrophage infiltration, inflammation[86]	Ref.[87,88]
Primary aldosteronism	Excess aldosterone	Subtype specific features[14]; hypertension, hypokalemia, insulin resistance, impaired glucose tolerance, increased cardiovascular risk[89]	Increased fibrosis, inflammation, altered adipokine secretion[38,90]	Ref.[38,91]
Adrenocortical carcinoma	Variable; often cortisol and/or androgen excess	Features of Cushing syndrome and/or virilization, metabolic syndrome features if hypercortisolism[92]	Increased peri-adrenal adipose tissue mass, potential tumor-induced fibrosis and altered adipokine profiles in dependence of the hormone secreted	Ref.[93,94]
Non-functional adenomas	None significant	Often incidental; might be associated with mild metabolic alterations if subclinical present	Minimal direct effects unless subclinical hypercortisolism induces changes	Ref.[93]

Abbreviations: AT, adipose tissue; peri-AT, peri-adrenal adipose tissue.

of hypercortisolism correlates with higher visceral adiposity.[87] In patients with active CS, hypercortisolism induced PRAT adipocyte hypertrophy, which is associated with increased macrophage infiltration and elevated leptin levels, as well as reduced adiponectin levels.[86] Another study identified higher leptin levels in peri-AT than in PRAT and subcutaneous AT in patients with CS.[34]

Primary bilateral macronodular adrenal hyperplasia (BMAD) is a rare cause of CS, often misdiagnosed as bilateral adrenal incidentalomas with subclinical cortisol production. Interestingly, BMAD frequently occur alongside myelolipoma, especially those associated with food-dependent (glucose-dependent insulinotropic polypeptide-dependent) hypercortisolism, due to *KDM1A* mutations.[97-99] However, the mechanisms by which these 2 lesions develop in parallel and influence each other remain unknown. Paradoxically, leptin stimulates cortisol secretion in nutrition-dependent BMAD.[100] Moreover, BMAD tissue expresses abnormal levels of ACTH.[101] It is therefore conceivable that adrenal cortex cells influence intra-adrenal adipocytes via a paracrine mechanism involving locally produced ACTH.[102,103]Reciprocally, AT may activate cortisol production through leptin release.

It is well known that acute or prolonged glucocorticoid administration decreases C-reactive protein (CRP), IL-6, and TNF-alpha (TNF-α). However, long-term hypercortisolism is characterized by chronic, low-grade inflammation.[88,104,105] Even after achieving a long-term cure, patients who have experienced CS exhibit a persistent accumulation of central fat, similar to that seen in active hypercortisolism, associated with an unfavorable adipokine profile and a state of low-grade inflammation.[88] Moreover, amelioration of visceral fat mass cannot be achieved in all patients, suggesting the presence of a potentially persistent epigenetic mechanism.[88,106] Compared to body mass index (BMI)-matched controls, patients with CS exhibit an increased number of infiltrating macrophages in subcutaneous AT and PRAT.[86,107] Macrophages stimulate expression of pro-fibrotic factors and interfere with the differentiation of preadipocytes, thus promoting AT fibrosis. Excess exposure to GC also has a pro-fibrotic effect on AT, which requires the presence of macrophages.[108] Consistently, chronic exposure to endogenous GC results in increased oxidative stress, inflammation, and fibrosis in PRAT.[12]

The adipokine leptin may promote proliferation and invasion of cancer cells by the activation of pathways such as phosphoinositide 3-kinases, mitogen-activated protein kinase (MAPK), and signal transducer and activator of transcription 3 (STAT3), while adiponectin may inhibit tumor growth and spread by inhibition of pathways such as nuclear factor kappa-light-chain-enhancer of activated B (NF-κB), STAT3, and mammalian target of rapamycin (mTOR).[109,110] However, studies examining effects of adipokines on adrenal tumors are mostly lacking. Hypercortisolism lead to changes in the levels of circulating adipokines, with higher fatty acid-binding protein 4 (FABP4), retinol-binding protein 4 (RBP4), and resistin levels compared to healthy controls.[111,112] Additionally, leptin expression was significantly higher in peri-AT than in PRAT or subcutaneous AT in patients with CS, while adiponectin expression was significantly lower.[34] Plasma leptin levels are also elevated in patients with CS and decrease following tumor resection.[113] Although fasting inhibits leptin secretion in healthy subjects, inhibitory effects of short-term fasting are less pronounced in patients with CS.[114] Leptin is known to decrease the corticotropin-stimulated release of steroids in vitro,[115] potentially providing a hint for an important feedback loop and illustrating the direct interaction between tumor, AT, and adrenal.

Primary aldosteronism

Primary aldosteronism is characterized by the autonomic secretion of aldosterone caused by unilateral or bilateral adrenal lesions, associated with fundamental metabolic consequences.[116,117] Compared to patients with essential hypertension, patients with PA exhibit a higher prevalence of insulin resistance, impaired glucose tolerance, and type 2 diabetes.[89] Excess aldosterone promotes AT dysfunction, inflammation, and fibrosis.[118] Furthermore, visceral obesity and altered adipokine secretion have been associated with increased cardiometabolic risk

observed in this population.[119,120] For example, APAs are associated with obesity in males, but not in females,[121] which may be related to the increased prevalence of *KCNJ5* mutations in females compared to males.[122,123] Furthermore, patients with bilateral PA present with a higher BMI and greater visceral adiposity than patients with unilateral disease,[14] reflecting the heterogeneity of metabolic characteristics across different PA subtypes, which are not yet fully understood. Treatment with MR agonists (eplerenone or spironolactone) lead to a significant reduction in VAT in these patients.[124] Adipocytes adjacent to APAs exhibit a browning phenotype, as evidenced by smaller adipocyte size and higher *UCP1* expression.[91] The authors of this study proposed the following mechanism: APA cells release retinoic acid, which promotes tissue browning and leads to the release of lactate by beige adipocytes, thereby increasing aldosterone production.[91] As outlined before, treatment with MR antagonists rather induce browning,[47,69,70] suggesting that aldosterone might not be the principal mediator of fat browning in patients with APA. In vitro studies revealed that only pharmacological concentrations of aldosterone reduced glucose uptake in adipocytes, suggesting: (1) insulin resistance in patients with PA may occur in compartments other than AT, and/or (2) it may depend on secondary factors, such as retinoic acid.[125] RNA sequencing revealed a downregulation of inflammation-associated pathways in SAT and peri-AT of patients with APA compared to patients with non-functional adrenal adenomas, while steroid-related pathways were upregulated, particularly in peri-AT of patients with *KCNJ5*-mutant APAs, which suggest a paracrine actions of aldosterone.[90] Moreover, cortisol co-secretion has been reported in up to 30% of patients with PA,[126,127] which might furthermore affect the adipose tissue phenotype in these patients.

Leptin expression in the PRAT was significantly higher in patients with APAs compared to patients with non-functional adenomas.[34] Leptin receptor (LEP-R) levels in APA tissues correlate positively with plasma aldosterone concentrations in these patients.[128,129] However, expression of the adiponectin receptor 1/2 (AdipoR1/2) and LEP-R is significantly lower in benign adrenal neoplasms compared to adrenocortical carcinomas (ACCs).[130] Aldosterone excess in patients with PA is furthermore associated with elevated resistin levels and cardiac alterations, independently of the presence of metabolic syndrome.[119] Moreover, PRAT of patients with APA exhibites significantly higher levels of IL-6, TNF-α and of genes related to fibrosis compared to normotensive individuals and patients with essential hypertension.[38] Whether these effects are related to increased macrophage infiltration, as in CS, is largely unknown.[38] In rats, it has been shown that administration of aldosterone plus salt mediates an inflammatory M1 macrophage phenotype and increased renal fibrosis via activation of mineralocorticoid receptors.[131] This suggests that APAs induce PRAT dysfunction associated with a pro-inflammatory and fibrotic state that can worsen cardiovascular impairment.

Adrenocortical carcinoma

Adrenocortical carcinomas often produce excess steroid hormones, most commonly cortisol and androgens, leading to clinically overt endocrine syndromes such as CS or virilization. The clinical presentation of patients with ACCs greatly depends on whether the tumor is hormonally active or "non-functional."[92] Metabolic effects and effects on peri-AT of the cortisol or aldosterone (rare) excess in these patients have already been discussed above. Additionally, in rare cases, ACCs can release estrogen, which can lead to feminization. Under physiological conditions, estrogen promotes lipolysis and inhibits adipogenesis.[132] Thus, estrogen enhances insulin sensitivity.[133] Androgens also play a critical role in AT homeostasis, by improving insulin sensitivity and glucose tolerance and by regulating the expression of various adipokines and regulating lipolysis.[134] However, the impact of ACC-driven androgen or estrogen excess on adipocytes and metabolism remains unknown.

A correlation has been found between an increase in intra-abdominal fat tissue and a reduced survival rate in patients with ACC.[135] Moreover, mixed cortisol/androgen-secreting ACCs are associated with worse overall survival compared to non-secreting ACCs, while cortisol or androgen secretion alone is not associated with worse overall survival.[136] Patients with ACC have higher IL-6, TNF-α and monocyte chemoattractant protein 1 (MCP1) serum levels compared to healthy controls, indicating similar to patients with CS a pro-inflammatory state.[93] However, little is known about the interaction of adipocytes and ACCs.

Monotherapy with mitotane is the first-line treatment for less aggressive ACCs after surgery, while patients with more aggressive forms of the disease are treated with mitotane plus chemotherapy.[137] However, due to its lipophilic nature, mitotane concentration is 200-fold higher in AT than in plasma.[138] Therefore, high dosages of mitotane are required to reach the therapeutic plasma concentration, which result in several adverse effects.[139] For example, mitotane has profound impact on lipid levels marked by increased total, low-density lipoprotein and high-density lipoprotein (HDL) cholesterol levels in more than half of the patients.[140,141] To the best of our knowledge, no studies have investigated the influence of BMI or body fat distribution on how ACC patients respond to mitotane treatment, though including these factors could improve outcomes and reduce side effects. Overall, ACC–adipose crosstalk remains poorly understood. Transcriptomic profiling of peri-AT alongside tumor hormone status and clinical parameters, as well as analysis of adipokine changes during rapid ACC progression, could provide valuable insights.

AT–adrenal medulla interactions

Catecholamines are well known to stimulate lipolysis by binding to β-adrenergic receptors expressed on adipocytes,[42,142] which leads to increased activity of adenylyl cyclase, resulting in evaluated levels of cyclic adenosine monophosphate (cAMP)[143] (Figure 2). Cyclic adenosine monophosphate further activates protein kinase A (PKA) that leads to phosphorylation of downstream targets including hormone-sensitive lipase. Hormone-sensitive lipase is capable of breaking down triacylglycerol to diacylglycerol, but to a lesser extent than the adipose triglyceride lipase (ATGL). Protein kinase A phosphorylates perilipin, which is associated with the lipid droplet in the basal state and impedes ATGL access and activity.[144] Insulin and GC furthermore affect this pathway by altering cAMP levels.[143,145] The activation of PKA further lead to an activation of rapamycin-sensitive mTOR complex 1 (mTORC1)[146] and p38 MAP kinase, resulting in the induction of target genes involved in fat browning (UCP1 and Pparg coactivator 1 alpha (PGC1α)).[42] Furthermore, co-culture experiments revealed that catecholamines block vesicle transport and secretion of leptin and resistin via β-adrenergic receptors, whereas leptin and resistin promote vesicle transport and secretion of catecholamines via PKA, protein kinase C (PKC), MAPK kinase, and Ca^{2+}-dependent signaling

pathways.[39] Leptin is secreted mainly by white adipocytes and stimulates the synthesis of catecholamines,[147,148] while catecholamines reduce leptin production.[149-151] Additionally, β-adrenergic stimulation of AT, rather than macrophages, seems to be responsible for enhanced plasma IL-6 concentrations observed in obesity.[152] Interleukin-6 is known to modulate adrenal steroid production indicating a crosstalk between AT and adrenal cortex.[153,154]

Approaches to promote energy consumption through the induction of thermogenesis are of high clinical relevance, especially given the widespread prevalence of obesity. β3-Adrenergic receptor is highly expressed in human BAT and WAT, as well as in other tissues such as the gallbladder, gastrointestinal tract, and prostate.[155] Therefore, various β3-agonists have been investigated for the treatment of obesity due to their potential appetite-suppressing and thermogenic effects.[156] None of the investigated agonists, however, advanced beyond clinical phase II due to a lack of efficacy and cardiovascular side effects, mainly caused by insufficient selectivity of available agonists.[157] While short-term exposure to high doses of β3-adrenergic agonist mirabegron leads to activation of BAT, catecholamine-secreting tumors (pheochromocytomas), as well as long-term exposure to mirabegron even promote fat browning.[156] To further evaluate the therapeutic potential for obesity and metabolic syndrome, more selective and potent β3-adrenergic receptor agonists with fewer off-target effects are needed.

AT–PCC interactions

Excessive catecholamine production by adrenal medullary PCC triggers a β3-adrenergic response that activates BAT and peri-AT browning.[28,36] This promotes a hypermetabolic state associated with increased glycogenolysis, lipolysis, and the release of proinflammatory cytokines.[10] Patients with functional PCCs exhibit higher prevalence of BAT activation[9,158] and weight gain after PCC resection has been observed.[11] The presence of active BAT is associated with higher plasma NE levels and decreased overall survival in patients with PCC.[159,160] Moreover, patients with BAT activation seem to be younger.[158] However, there is no significant correlation between changes in plasma catecholamines or metanephrines and changes in fat mass.[161,162] A meta-analysis identified elevated catecholamine levels, particularly NE/normetanephrine, to be associated with the presence of activated BAT on imaging in patients with PCC.[163]

Brown adipose tissue activation in PCC exhibits regional distribution differences, with stronger activation closer to the tumor (peri-AT) than further away from the tumor (subcutaneous).[40] This may be due to a hormonal gradient or to differences in the response of AT at different sites to adrenal signaling. Surprisingly, no difference in 18F-fluorodeoxyglucose uptake by the peri-renal AT between the side of the PCC and contralateral side has been observed.[9] Moreover, pheochromocytomas and paragangliomas (PPGLs) are genetically heterogeneous tumors with a strong genotype–phenotype correlation, but no difference in the prevalence of BAT activation was observed between sporadic cases or patients with succinate dehydroxygenase (SDHx) or von Hippel–Lindau (VHL)-related PPGLs.[9] Discrepancies between studies on the prevalence of activated BAT in patients with PPGLs and a possible correlation with excess catecholamine/NE[9,11,158-160,162,163] could be related to differences in the timing and implementation of an adrenergic receptors blockade. Since intraoperative mobilization of the tumor often leads to a sudden rise in blood pressure in these patients due to the release of catecholamines, guidelines recommend preoperative treatment of symptomatic patients with α-adrenoreceptor antagonists.[164,165] Depending on when adrenergic receptor blockade is initiated, this might affect the results.

Adrenergic stimulation triggers a series of molecular events through activation of β-adrenergic receptor signaling in AT, including altered gene expression and splicing regulation, ultimately leading to browning of AT, increased thermogenesis and enhanced metabolism.[84] In AT of patients with PCC, elevated expression of genes associated with mitochondrial heat production (eg, UCP1 and CKMT1A/B) and lipid and carbohydrate catabolism is observed, while pro-inflammatory pathways are decreased.[84] Peri-renal brown adipocytes in patients with PCC recapitulate activated classical brown adipocytes with the reduced expression of markers selective for beige adipocytes (CD137 and TBX1).[166] In retroperitoneal VAT of patients with PPGL *UCP1* expression correlate negatively with the BMI and positively with HDLc levels.[167]

Fibroblast growth factor-21 (FGF21) plays a systemic role by promoting glucose uptake, insulin secretion, and brown adipogenesis.[168,169] NE activates the transcription of the *FGF21* through a cAMP-dependent PKA- and p38 MAPK-mediated mechanisms in BAT.[170,171] FGF21 is released from BAT into circulation during thermogenic activation.[170] Visceral adipose tissue of patients with PCC significantly expressed *FGF21* and *UCP1* with a positive correlation, suggesting that FGF21 is involved in human BAT activation in these patients.[169] Adrenomedullin (ADM), a peptide released, for example, by chromaffin cells of the adrenal medulla or PCCs, may also be involved in tumor–AT interactions since ADM causes browning of adipocytes in proximity to breast cancer cells.[172] However, it is not known whether this effect plays a role in browning of peri-AT in patients with PCC, which even presents with elevated plasma ADM levels.[173]

Adiponectin expression is significantly higher in BAT than in WAT around PCC, and urinary metanephrine levels correlate positively with UCP1 expression in BAT.[174] *AdipoR1* and *AdipoR2* expression is significantly higher in PCC than in adrenocortical tumors.[130] Moreover, *AdpR1* expression is higher in epinephrine-producing PCCs than in NE-producing PCCs.[175] Leptin receptor is more frequently expressed in PCC than in ACCs,[130] but leptin does not appear to be involved in the regulation of cell proliferation in adrenal tumors.[176] Moreover, patients with PCC have higher mitochondrial content in peri-AT and significantly higher peridroplet mitochondria content, associated with increased energy expenditure.[177] Peridroplet mitochondria is a functionally independent subpopulation of mitochondria in AT involved in browning and energy metabolism. Up to one-third of PCC patients develop diabetes due to impaired glucose tolerance and insulin resistance.[178,179] Compared to patients with non-functional adenomas, the peri-AT of patients with PCC exhibits reduced phosphorylated AMP-activated protein kinase expression, increased expression of pyruvate dehydrogenase kinase (PDK4), pIRS1, and oxidative stress markers.[179] Due to PDK4's involvement in glucose uptake, it may play a role in the catecholamine-induced insulin resistance in patients with PCC.

Conclusion and perspectives

Adrenal–AT interactions play a pivotal role in regulating systemic energy homeostasis, stress responses, and metabolic health. Adrenal tumors are associated with impaired adrenal

hormone secretion, which leads to dysfunction of AT, promoting visceral obesity, insulin resistance, and cardiovascular complications. Moreover, chronic stress also impairs this tightly regulated system, contributing to the widespread prevalence of obesity, insulin resistance, and cardiovascular disease in our society. Targeting this bidirectional system therapeutically may not only be a promising approach to improve care for patients with adrenal tumors, but it may also help to cure obesity and type 2 diabetes.

Emerging evidence indicates that peri-AT can influence adrenal tumor biology via endocrine, paracrine, and immune signaling, affecting tumor progression and therapy response. However, the precise mechanisms remain unclear. Multiomics studies of matched tumor and AT correlated with clinical parameters are needed to identify novel targets, mitigate metabolic and cardiovascular risk, and enable personalized management. Whether modulating adipose inflammation or browning can improve adrenal disease outcomes remains unknown, highlighting the need for further translational research into this complex crosstalk.

Authors' contributions

Mingyan Jiang (Conceptualization [lead], Writing—original draft [lead], Writing—review & editing [equal]), Ulrich Stifel (Conceptualization [equal], Writing—review & editing [equal]), Nicole Bechmann (Conceptualization [lead], Funding acquisition [lead], Project administration [lead], Supervision [lead], Visualization [lead], Writing—original draft [equal], Writing—review & editing [lead]), Stefan R. Bornstein (Funding acquisition [equal], Supervision [equal], Writing—review & editing [equal]), Hervé Lefebvre (Conceptualization [equal], Writing—review & editing [equal]), and Matthias Blüher (Conceptualization [equal], Writing—review & editing [equal])

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