Curr Hypertens Rep (2016) 18:20
DOI 10.1007/s11906-016-0626-9

HYPERTENSION AND OBESITY (E REISIN, SECTION EDITOR)

# Aldosterone Production and Signaling Dysregulation in Obesity

**Andrea Vecchiola**[1,2] · **Carlos F. Lagos**[1,3] · **Cristian A. Carvajal**[1,2] · **Rene Baudrand**[1] · **Carlos E. Fardella**[1,2]



**Abstract** In the past decades, we have extended the view of aldosterone effects beyond epithelial tissues. New evidence regarding the aldosterone/mineralocorticoid receptor (MR) pathway in active metabolic tissues, including adipose tissue, has confirmed its pathogenic role in systemic inflammation, endothelial dysfunction, insulin resistance, and dyslipidemia. Obesity, a current epidemic worldwide, increases aldosterone production by several adipocyte factors such as leptin but is also associated with local aldosterone production. In addition, obesity can modulate MR activation leading to signaling dysregulation and a pro-inflammatory profile of adipocytes. Current knowledge have deciphered that this phenotypical differences of obesity may be explained, at least in part, by novel non-genomic activation of MR, new inducers of aldosterone synthesis, and probably by several epigenetic modifications. In addition, with the understanding of the complex interplay of obesity, hormones, and receptors, targeted pharmacological therapy is expected and is currently under active research.

**Keywords** Aldosterone · Adipose tissue dysfunction · Mineralocorticoid receptor · Metabolic syndrome · GPR30 · Aldosterone synthase · Renin-angiotensin-aldosterone system · Adiponectin · Leptin · Obesity

This article is part of the Topical Collection on *Hypertension and Obesity*

✉ Carlos E. Fardella
cfardella@med.puc.cl

[1] Department of Endocrinology, School of Medicine, Pontificia Universidad Católica de Chile, Lira 85, 5th Floor, Santiago 8330074, Chile

[2] Millenium Institute on Immunology and Immunotherapy IMII, Santiago, Chile

[3] Facultad de Ciencia, Universidad San Sebastián, Santiago, Chile

## Introduction

Aldosterone is known as a mineralocorticoid hormone involved in the regulation of electrolyte balance and volume homeostasis in epithelial cells [1]. By acting on kidney distal nephron, aldosterone promotes sodium reabsorption, water retention, and potassium and magnesium loss, modulating the extracellular space volume and blood pressure [2]. The epithelial cells of the kidney express the mineralocorticoid receptor (MR) a nuclear receptor that after binding to aldosterone translocates to the cell nucleus and modulates expression of specific "aldosterone-induced" proteins that regulate electrolyte and fluid balance [3].

The main regulator of aldosterone secretion is the renin-angiotensin system [4]. Renin is synthesized by the juxtaglomerular cells of the kidney in response to low circulating blood volume, decreased renal perfusion, or reduced tubular sodium chloride concentration. Renin catalyzes the conversion of angiotensinogen to angiotensin I (Ang I); this is, in turn, converted to angiotensin II (Ang II) by the angiotensin-converting enzyme. Ang II induces the synthesis of aldosterone by the zona glomerulosa in the adrenal cortex through to AT1 receptor. Potassium levels and the adrenocorticotropic hormone can also regulate aldosterone levels [5].

Once aldosterone is produced and secreted on epithelial cells from the renal tubule, vascular smooth muscle cells, or adipose tissue [6, 7], it exerts most of its biological activities through binding to the MR, a member of the steroid receptor family [8]. After binding to the MR, the complex dimerizes and translocates to the nucleus where it induces the expression of genes related to water and salt regulation, such as epithelial 3 sodium channel (ENaC), sodium-potassium ATPase, and serum/glucocorticoid regulated kinase 1 (SGK1). The main goal of these processes is to maintain the body blood pressure in a normal range by means of water and electrolyte homeostasis control [9, 10].

Published online: 02 February 2016

During the past years, studies showing the expression of MR in tissues such as the heart [11], blood vessels [12], brain [13], and immune cells [14–17] have extended the view of aldosterone acting beyond epithelial tissues. Thus, aldosterone is not only linked to systemic inflammation, endothelial dysfunction, increased vascular stiffness, hypertension, and cardiac hypertrophy but also to impaired pancreatic β-cell function, skeletal muscle insulin sensitivity, liver deficiency, and increased release of pro-inflammatory cytokines from the adipose tissue leading to impaired glucose tolerance and dyslipidemia [18–20].

## Aldosterone and Obesity

Aldosterone has been linked with obesity and metabolic syndrome (MetS) that is a combination of interrelated risk factors of metabolic origin, including arterial hypertension, dyslipidemias, glucose intolerance, abdominal obesity, and a pro-inflammatory and prothrombotic state [21]. Patients with central obesity have higher levels of aldosterone, which have been associated with the development of MetS. Recently, aldosterone dysregulation was associated with MetS and cardiometabolic risk factors [22•]. On the other hand, urinary aldosterone, as a proxy of aldosterone daily production, has been linked with central obesity and higher adipose tissue [23].

Primary aldosteronism (PA) showed a high prevalence of MetS proposing a negative effect of aldosterone excess on glucose metabolism, suggesting that higher rates of cardiovascular events in PA than in essential hypertensives might also be secondary to an increase of the MetS in the former condition [24]. Moreover, The Framingham Offspring Study demonstrated an association of aldosterone levels with the development of MetS and with the longitudinal change of its components, suggesting that aldosterone may play a key role in mediating metabolic risk [25]. Observations that aldosterone might have detrimental effects on glucose metabolism and/or insulin action were focused on the similarities between the action of aldosterone and glucocorticoids and in the role of hypokalemia as a link between aldosterone and insulin secretion [26–30]. Mosso et al. showed that PA patients have lower HOMA-bF index and C-peptide levels and a negative correlation between HOMA-bF and ARR, suggesting a decrease in insulin secretion or production secondary to aldosterone excess. The significant increases of the C-peptide and insulin after spironolactone treatment support the hypothesis that this effect could be mediated by aldosterone [31].

Aldosterone plasma levels have been shown to be associated with insulin resistance (IR), characterized by a reduced ability of insulin to inhibit the production of glucose from the liver and to promote glucose uptake in adipose tissue and skeletal muscle in normotensive healthy subjects independent of traditional risk factors [32]. Although the pathophysiological determinants linking aldosterone excess and IR are still largely unknown, it is known that PA patients display an increased incidence of IR mediated by the decreased gene expression of lipid metabolism genes phosphoenolpyruvate carboxykinase, perilipin, adiponectin, and peroxisome proliferator-activated receptors (PPARγ) in the visceral adipose tissue (VAT) compared to age-, sex-, and BMI-matched controls [33].

Excess adiposity has been associated with elevated urinary aldosterone levels [23], as well as higher plasma aldosterone has been associated with obese subjects' essential hypertension [34]. Engeli et al. demonstrated that 70 % of obese women with weight loss showed a reduction of at least one of the renin-angiotensin-aldosterone system (RAAS) component [35]. Further, animal studies have also shown that MR expression is increased in obesity, which suggests that in this disease there is a combination of higher ligand and receptor overexpression in its pathophysiology [36•].

Today it is known that components of the RAAS are produced by adipocytes [36•, 37]. In addition to angiotensin II (Ang II), adipocytes secrete mineralocorticoid-releasing factors that stimulate steroidogenesis in human adrenocortical cells which might explain the higher aldosterone levels often observed in obese subjects [36•, 38–40]. Fatty acid oxidation products, or endogenous ones from adipocytes, could stimulate aldosterone synthesis [41]. The peroxidation product of linoleic acid, 12,13-epoxy-9-*oxo*-10 (*trans*)-octadecanoic acid (EKODE), stimulates the production of aldosterone by isolated rat zona glomerulosa cells, suggesting that free fatty acids could stimulate synthesis and release of aldosterone in adipocytes independently of angiotensin II (Fig. 1). Interestingly, in humans, EKODE plasma levels correlated with aldosterone plasma levels [41], while a positive correlation between aldosterone and the adipocyte-derived hormone leptin has recently been established [42].

Recently, Huby et al. described that leptin is a direct regulator of aldosterone secretion, regulating aldosterone synthase (CYP11B2) expression and production and promoting endothelial dysfunction and cardiac fibrosis [43•]. On the other hand, aldosterone synthase-deficient mice (As (−/−)) fed on a high-fat diet display better profile in insulin secretion, adipocyte size, and fatty liver than wild type. These results provide further evidence for a novel role of aldosterone in obesity-induced beta cell dysfunction, hepatic steatosis, and adipose inflammation [44].

In addition to the well-known effect of sodium and potassium on aldosterone regulation, new mechanisms include inadequate aldosterone feedback of adipocyte-releasing factors and alternative MR modulators such as caveolin-1 or Rac1 [45, 46]. With this new information regarding the complexity

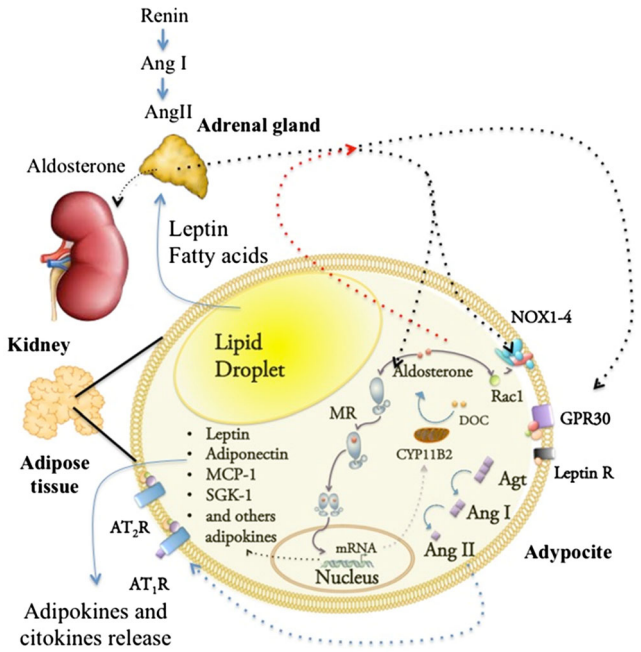


**Fig. 1** Aldosterone signaling in the adipocyte. In the adipocyte, aldosterone income from both the adrenal gland and in situ generated by the adipocyte by its own RAAS axis machinery may signal through a variety of genomic and non-genomic mechanisms and molecular pathways affecting adipose physiology. Aldosterone may act through a non-genomic pathway by binding to the membrane-bound GPR30 receptor or by inducing oxidative stress through Rac1 within or independently of the NOX complex. Otherwise, aldosterone may act through a genomic pathway by ligand-independent Rac1-mediated MR activation or by classical aldosterone-mediated MR activation along with transcription factors induced by non-genomic pathways induction and promote gene transcription of cytokines and adipokines, which can be secreted and induce adipocyte dysfunction. Aldosterone-releasing factors derived from these adipocytes, such as leptin and free fatty acids, have been shown to modulate aldosterone synthesis in the adrenal gland

of the aldosterone/MR pathway, is not surprising that contemporary environmental factors such as high sodium intake and some prevalent non-communicable diseases such as obesity can disturb the established aldosterone homeostasis, resulting in secretory and signaling dysregulation leading to several cardiometabolic disorders.

## Aldosterone in the Adipocyte Function and Differentiation

The action of MR on adipose tissue was reported by Zennaro et al. in 1998, using a transgenic mice model that overexpress MR promoter activity leading to liposarcoma development, thus demonstrating that MR was transcriptionally active in adipocytes [47]. Then, the effect of aldosterone/MR on adipose tissue identified an important role in T37i cells differentiation. This cells in the presence of aldosterone showed a white rather than brown phenotype with accumulation of intracytoplasmic lipid droplets, intracellular triglyceride induction, and inhibition of UCP1 expression and thermogenesis, effects that were reverted by MR antagonists but not by GR antagonist [48]. The treatment with aldosterone in this cell line also enhanced early adipogenic gene markers, confirming the activation of the differentiation process [49].

The role of MR and aldosterone in white fat differentiation was also explored by Caprio et al. [50], where they showed that aldosterone was able to induce white adipose differentiation in 3T3-L1, promoting intracellular accumulation of lipid droplets and induction of PPARγ and adipokines such as adiponectin, leptin, and resistin; these effects were reversed by the MR blocker spironolactone. Moreover, individuals with hypertrophic adipocytes have elevated pro-inflammatory factors including IL-6, IL-8, and monocyte-chemotactic-protein-1 (MCP-1) [51] and reduced adiponectin and IL-10 [51–53].

Studies in animal models has demonstrated that the activation of MR contributes to the inflammatory state in obesity increasing pro-inflammatory cytokines gene expression such as tumor necrosis factor-α (TNF-α), MCP-1, and prothrombotic factor plasminogen activator inhibitor type 1 (PAI-1), compared with lean, wild-type mice effect, and this phenotype was prevented by eplerenone [54]. In addition, eplerenone significantly reduced macrophage infiltration and reactive oxygen species production in adipose tissue [55]. Taken together, these results suggest that MR activation contributes to the changes in adipose tissue that promote low-grade inflammation.

Recent findings have also emphasized the interplay existing between gluco- and mineralocorticoid hormones and their respective receptors in the modulation of adipose tissue biology, an active topic of research that is beyond the scope of this review [56, 57•]. To date, adipose tissue function had not been studied in MR knockout mice neither in the knockdown MR transgenic rodents, since these models have been focused on MR activation in epithelial tissues [58–62].

## Non-genomic and Epigenetic Modulation of Aldosterone Signaling in Adipocytes

Steroid hormone receptors also induce rapid extranuclear signaling effects including the activation of kinase signaling cascades and increases in second messenger production without transcriptional activity. Aldosterone binds to the MR and also mediates rapid non-genomic effects through the transactivation of the epidermal growth factor receptor (EGFR), through phosphorylation signaling by the mitogen-activated protein kinase (MAPK) cascades [63], as demonstrated in renal, cardiovascular, colonic, and brain tissues through the sensitivity of these responses to MR antagonists such as spironolactone or eplerenone [64].

Thus aldosterone, through genomic and non-genomic actions, contributes to induce several abnormalities beyond classic renal and vascular effects such as impaired beta cell function, as well as reduced skeletal muscle and adipose tissue insulin sensitivity [64–66]. Many of the rapid non-genomic actions of aldosterone are also mediated by GPR30 (or GPER-1), a G-protein coupled receptor [67] (Fig. 1). In human adrenal cortex and aldosterone-producing adenoma cells, GPR30 is the second most expressed receptor [68]. Interestingly, GPR30 deficiency in male mice results in insulin resistance, dyslipidemia, and a pro-inflammatory state [69]. The activation of GPR30 by the natural ligand 17β-estradiol (E2), and the specific agonist G1, was shown to inhibit lipid accumulation in 3T3-L1 cells, while such inhibition was reversed upon knockdown of GPR30 using specific siRNA or GPR30 antagonist [70].

Obesity has emerged in the last years as a potential contributor for the epigenetic regulation of gene expression. Epigenetic modifications included DNA methylation, post-translational histone modifications, and non-coding RNA-mediated silencing processes [71, 72]. These mechanisms, together with other transcriptional regulatory events, ultimately regulate gene activity and expression during development and differentiation or in response to nutritional and environmental stimuli [72]. However, it is unknown whether obesity affects the epigenetic regulation of different genes involved in adipose tissue dysfunction through aldosterone and/or MR activation.

Recently, Demura et al. showed that angiotensinogen (AGT) gene is an epigenetic-regulated gene in adipocytes, where DNA methylation negatively regulates AGT expression, which dynamically changes in response to continuous AGT promoter stimulation [73•]. High-salt intake and excess circulating aldosterone cause DNA demethylation around the CCAAT enhancer-binding protein-binding sites, thereby converting the phenotype of AGT expression from an inactive to an active state in visceral adipose tissue [74]. Evidences of methylation were also found in key genes regulating aldosterone biosynthesis (i.e., CYP11B2, AVPR1a, and PRKCA). These genes that regulate steroidogenic signals and synthesis in adrenocortical cells were differentially methylated: AVPR1a and PRKCA were downregulated and hypermethylated, and CYP11B2 was upregulated and hypomethylated [75].

On the other hand, microRNA (miRNA) regulation has been found in genes regulating RAAS. In 2013, Robertson et al. showed that aldosterone synthase (CYP11B2) 3′UTR is regulated by miR-24, miR-125a-5p, and miR-125b in adrenal cells [76]. Similarly, post-transcriptional regulation of MR gene expression in kidney is modulated by miR-124 and miR-135a [77]. In a rodent and human vascular smooth muscle cells (VSMC), the expression of AT1R is downregulated by miR-483-3p, which is a potential negative regulator of steady-state levels of RAAS acting directly over 3′UTR region of four different RAAS genes [78]. All these recent evidences support the potential epigenetic regulation by methylation CpG or miRNA of RAAS genes in adipose tissue and encourage further studies in this field.

## Targeting Aldosterone Production and Signaling Pathways in Adipocyte

Despite the fact that obesity is a worldwide public health problem, current antiobesity therapy has only modest effects in body weight and associated cardiometabolic disorders [79–81]. Thus, targeting the pathogenic role of aldosterone signaling in adipose tissue is an interesting strategy. Considering the integrated pathways between different organs as well as the autocrine/paracrine action of these compounds on adipocyte biology, the adipocyte RAAS system regulation, aldosterone secretion, MR blockade, and adipokine receptors modulation emerge as targets to unravel the molecular mechanism of aldosterone action in adipocytes and thus identify novel therapeutic approaches.

As explained above, fat cells appear to stimulate aldosterone secretion, but aldosterone also appears to mediate adipocyte differentiation, and the increase in adipocyte mass may generate an autocrine-positive feedback loop for RAAS components [82, 83]. Several angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) reduce the secretion of aldosterone or increase adiponectin levels [84–86]. However, despite treatment with ACEi or ARBs, the plasma aldosterone level of classes 2 and 3 obese patients was higher than non-obese and class 1 obese patients probably because of aldosterone "breakthrough" [87, 88]. Another RAAS system player, Ang 1–7, had an ameliorating effect in obesity, adiposity, and myogenic and adipogenic differentiation [89, 90]. On the other hand, aldosterone synthase (CYP11B2) inhibition reduces aldosterone levels. However, inhibition of the highly similar enzyme CYP11B1, responsible for the production of cortisol, must be avoided because of the resulting impairment of the cortisol-induced stress response [91•]. Next-generation CYP11B2 inhibitors are currently under development, showing improved selectivity index and reduction of aldosterone levels in humans [92]. The recently solved crystal structure of human CYP11B2 provides a structural basis for the design of novel aldosterone synthase inhibitors, and the development of suitable surrogates for the human enzymes will provide superior in vitro assay systems for bioactivity evaluation [93•, 94].

In relation to aldosterone/MR pathway in mice, interestingly MR antagonists have shown to control HF diet-induced impairment in glucose tolerance and prevent body weight gain

and white fat expansion [95]. However, in a small double-blind, placebo-controlled, randomized clinical study in rather healthy obese non-diabetic (NCT01406015), spironolactone 50 mg daily versus placebo for 6 weeks showed only decreased median systolic blood pressure with no effect on other metabolic disorders [96••]. Thus, future studies in selected high-risk subjects with confirmed aldosterone dysregulation are warranted.

Finally, modulating adipokines that have a pathogenic role in obesity is a novel pharmacologic strategy. Enhanced leptin signaling elevated CYP11B2 expression and plasma aldosterone levels. The advancement into the structural and mechanistic aspects of leptin receptor (LR) activation allows a rational design of leptin receptors antagonists that may block obesity-induced increases in CYP11B2 and aldosterone [97, 98]. On the other hand, adiponectin secreted from adipocytes binds to adiponectin receptors AdipoR1 and AdipoR2 and exerts beneficial metabolic effects via activation of AMPK and PPAR-α pathways, respectively [99, 100]. The recently reported crystal structure of human AdipoR1 and AdipoR2 receptors provides a basis for the identification of novel adiponectin receptor agonists, that will help understanding the roles and mechanisms of the AdipoR1/AdipoR2 in lipid metabolism [101•]. Further studies will show the potential of these approaches to ameliorate obesity-related disorders.

## Conclusions

In the past decades, we have extended the view of aldosterone effects beyond epithelial tissues. New evidence regarding the aldosterone/MR pathway in active metabolic tissues, including adipose tissue, has confirmed its pathogenic role in systemic inflammation, endothelial dysfunction, insulin resistance, and dyslipidemia, which are clustered in obesity.

We have recently learned that adipocytes express MR and also secrete aldosterone. Thus, both in vitro and in vivo studies have demonstrated a role for the aldosterone and MR activation in adipose tissue differentiation and enhanced early adipogenic gene markers. Also, current knowledge have deciphered that obesity- associated metabolic disorders may be explained, at least in part, by novel non-genomic activation of MR, new inducers of aldosterone synthesis, such as leptin, and probably by several epigenetic modifications. With the understanding of this complex interplay of obesity, hormones, and receptors, novel targeted pharmacological therapy is under active research.

**Acknowledgments** This article was funded by CONICYT-FONDECYT grants No. 1130427, No. 1150437 and No. 1160695, IMII P09/016-F ICM, CORFO 13 CTi-21526-P1 grants.

**Compliance with Ethical Standards**

**Conflict of Interest** Dr. Carvajal reports grants and personal fees from Fondecyt No. 1130427, from Fondecyt No. 1150437, from IMII P09/016-F ICM, and from CORFO 13CTI-21526-P1.

Dr. Baudrand reports grants and personal fees from Fondecyt No. 1130427, and from Fondecyt No. 1150437.

Dr. Fardella reports grants and personal fees from Fondecyt No. 1130427, from Fondecyt No. 1150437, from IMII P09/016-F ICM, and from CORFO 13CTI-21526-P1.

Dr. Lagos reports grants and personal fees from CORFO 13CTI-21526-P1.

Dr. Vecchiola reports grants and personal fees from Fondecyt No. 1130427, from Fondecyt No. 1150437, from IMII P09/016-F ICM, and from CORFO 13CTI-21526-P1.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell. 2001;104(4):545–56.
2. Spat A, Hunyady L. Control of aldosterone secretion: a model for convergence in cellular signaling pathways. Physiol Rev. 2004;84(2):489–539. doi:10.1152/physrev.00030.2003.
3. Gomez-Sanchez E, Gomez-Sanchez CE. The multifaceted mineralocorticoid receptor. Compr Physiol. 2014;4(3):965–94. doi:10.1002/cphy.c130044.
4. Muller-Fielitz H, Lau M, Johren O, Stellmacher F, Schwaninger M, Raasch W. Blood pressure response to angiotensin II is enhanced in obese Zucker rats and is attributed to an aldosterone-dependent mechanism. Br J Pharmacol. 2012;166(8):2417–29. doi:10.1111/j.1476-5381.2012.01953.x.
5. Tomaschitz A, Pilz S, Ritz E, Obermayer-Pietsch B, Pieber TR. Aldosterone and arterial hypertension. Nat Rev Endocrinol. 2010;6(2):83–93. doi:10.1038/nrendo.2009.263.
6. Marver D, Kokko JP. Renal target sites and the mechanism of action of aldosterone. Miner Electrolyte Metab. 1983;9(1):1–18.
7. Jaffe IZ, Mendelsohn ME. Angiotensin II and aldosterone regulate gene transcription via functional mineralocorticoid receptors in human coronary artery smooth muscle cells. Circ Res. 2005;96(6):643–50. doi:10.1161/01.RES.0000159937.05502.d1.
8. NRN Committee. A unified nomenclature system for the nuclear receptor superfamily. Cell. 1999;97:161–3.
9. Fuller PJ, Young MJ. Mechanisms of mineralocorticoid action. Hypertension. 2005;46(6):1227–35. doi:10.1161/01.HYP.0000193502.77417.17.
10. Naray-Fejes-Toth A, Fejes-Toth G. The sgk, an aldosterone-induced gene in mineralocorticoid target cells, regulates the epithelial sodium channel. Kidney Int. 2000;57(4):1290–4. doi:10.1046/j.1523-1755.2000.00964.x.
11. Lombes M, Alfaidy N, Eugene E, Lessana A, Farman N, Bonvalet JP. Prerequisite for cardiac aldosterone action. Mineralocorticoid

receptor and 11 beta-hydroxysteroid dehydrogenase in the human heart. Circulation. 1995;92(2):175–82.
12. Takeda Y, Miyamori I, Inaba S, Furukawa K, Hatakeyama H, Yoneda T, et al. Vascular aldosterone in genetically hypertensive rats. Hypertension. 1997;29(1 Pt 1):45–8.
13. Zhou MY, Gomez-Sanchez CE, Gomez-Sanchez EP. An alternatively spliced rat mineralocorticoid receptor mRNA causing truncation of the steroid binding domain. Mol Cell Endocrinol. 2000;159(1–2):125–31.
14. Rickard AJ, Morgan J, Tesch G, Funder JW, Fuller PJ, Young MJ. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. Hypertension. 2009;54(3):537–43. doi:10.1161/HYPERTENSIONAHA.109.131110.
15. Rickard AJ, Young MJ. Corticosteroid receptors, macrophages and cardiovascular disease. J Mol Endocrinol. 2009;42(6):449–59. doi:10.1677/JME-08-0144.
16. Carvajal CA, Herrada AA, Castillo CR, Contreras FJ, Stehr CB, Mosso LM, et al. Primary aldosteronism can alter peripheral levels of transforming growth factor beta and tumor necrosis factor alpha. J Endocrinol Investig. 2009;32(9):759–65. doi:10.3275/6429.
17. Herrada AA, Contreras FJ, Marini NP, Amador CA, Gonzalez PA, Cortes CM, et al. Aldosterone promotes autoimmune damage by enhancing Th17-mediated immunity. J Immunol. 2010;184(1):191–202. doi:10.4049/jimmunol.0802886.
18. Calhoun DA, Sharma K. The role of aldosteronism in causing obesity-related cardiovascular risk. Cardiol Clin. 2010;28(3):517–27. doi:10.1016/j.ccl.2010.04.001.
19. Pimenta E, Calhoun DA. Aldosterone and metabolic dysfunction: an unresolved issue. Hypertension. 2009;53(4):585–6. doi:10.1161/HYPERTENSIONAHA.108.123406.
20. Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. Ann Intern Med. 2009;150(11):776–83.
21. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. Endocr Rev. 2008;29(7):777–822. doi:10.1210/er.2008-0024.
22.• Vaidya A, Underwood PC, Hopkins PN, Jeunemaitre X, Ferri C, Williams GH, et al. Abnormal aldosterone physiology and cardiometabolic risk factors. Hypertension. 2013;61(4):886–93. doi:10.1161/HYPERTENSIONAHA.111.00662. **This report presents new information, whether novel indices of aldosterone responses to dietary sodium modulation, could predict cardiometabolic risk factors. The integration of aldosterone suppression and stimulation would provide an improved representation of aldosterone physiology in disease states that could offer new insights in the pathogenesis and treatment of cardiometabolic derangements**.
23. Harada E, Mizuno Y, Katoh D, Kashiwagi Y, Morita S, Nakayama Y, et al. Increased urinary aldosterone excretion is associated with subcutaneous not visceral, adipose tissue area in obese individuals: a possible manifestation of dysfunctional subcutaneous adipose tissue. Clin Endocrinol. 2013;79(4):510–6. doi:10.1111/cen.12083.
24. Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, et al. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J Clin Endocrinol Metab. 2006;91(2):454–9. doi:10.1210/jc.2005-1733.
25. Ingelsson E, Pencina MJ, Tofler GH, Benjamin EJ, Lanier KJ, Jacques PF, et al. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. Circulation. 2007;116(9):984–92. doi:10.1161/CIRCULATIONAHA.107.708537.
26. Rowe JW, Tobin JD, Rosa RM, Andres R. Effect of experimental potassium deficiency on glucose and insulin metabolism. Metab Clin Exp. 1980;29(6):498–502.
27. Ferrannini E, Galvan AQ, Santoro D, Natali A. Potassium as a link between insulin and the renin-angiotensin-aldosterone system. J Hypertens Suppl. 1992;10(1):S5–10.
28. Luther JM. Effects of aldosterone on insulin sensitivity and secretion. Steroids. 2014;91:54–60. doi:10.1016/j.steroids.2014.08.016.
29. Luther JM, Brown NJ. The renin-angiotensin-aldosterone system and glucose homeostasis. Trends Pharmacol Sci. 2011;32(12):734–9. doi:10.1016/j.tips.2011.07.006.
30. Luther JM, Luo P, Kreger MT, Brissova M, Dai C, Whitfield TT, et al. Aldosterone decreases glucose-stimulated insulin secretion in vivo in mice and in murine islets. Diabetologia. 2011;54(8):2152–63. doi:10.1007/s00125-011-2158-9.
31. Mosso LM, Carvajal CA, Maiz A, Ortiz EH, Castillo CR, Artigas RA, et al. A possible association between primary aldosteronism and a lower beta-cell function. J Hypertens. 2007;25(10):2125–30. doi:10.1097/HJH.0b013e3282861fa4.
32. Garg R, Hurwitz S, Williams GH, Hopkins PN, Adler GK. Aldosterone production and insulin resistance in healthy adults. J Clin Endocrinol Metab. 2010;95(4):1986–90. doi:10.1210/jc.2009-2521.
33. Williams TA, Monticone S, Urbanet R, Bertello C, Giraudo G, Vettor R, et al. Genes implicated in insulin resistance are downregulated in primary aldosteronism patients. Mol Cell Endocrinol. 2012;355(1):162–8. doi:10.1016/j.mce.2012.02.007.
34. Rossi GP, Belfiore A, Bernini G, Fabris B, Caridi G, Ferri C, et al. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. J Clin Endocrinol Metab. 2008;93(7):2566–71. doi:10.1210/jc.2008-0251.
35. Engeli S, Bohnke J, Gorzelniak K, Janke J, Schling P, Bader M, et al. Weight loss and the renin-angiotensin-aldosterone system. Hypertension. 2005;45(3):356–62. doi:10.1161/01.HYP.0000154361.47683.d3.
36.• Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, et al. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. Hypertension. 2012;59(5):1069–78. doi:10.1161/HYPERTENSIONAHA.111.190223. **Adipocytes possess aldosterone synthase and produce aldosterone in an Ang II/Ang II type 1 receptor/calcineurin/nuclear factor of activated T-cells–dependent manner. identifying adipocytes as a putative link between aldosterone and vascular dysfunction in diabetes mellitus–associated obesity**.
37. Schinner S, Willenberg HS, Krause D, Schott M, Lamounier-Zepter V, Krug AW, et al. Adipocyte-derived products induce the transcription of the StAR promoter and stimulate aldosterone and cortisol secretion from adrenocortical cells through the Wnt-signaling pathway. Int J Obes. 2007;31(5):864–70. doi:10.1038/sj.ijo.0803508.
38. Nagase M, Yoshida S, Shibata S, Nagase T, Gotoda T, Ando K, et al. Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. J Am Soc Nephrol. 2006;17(12):3438–46. doi:10.1681/ASN.2006080944.
39. Lamounier-Zepter V, Ehrhart-Bornstein M, Bornstein SR. Mineralocorticoid-stimulating activity of adipose tissue. Best Pract Res Clin Endocrinol Metab. 2005;19(4):567–75. doi:10.1016/j.beem.2005.07.002.
40. Ehrhart-Bornstein M, Arakelyan K, Krug AW, Scherbaum WA, Bornstein SR. Fat cells may be the obesity-hypertension link: human adipogenic factors stimulate

aldosterone secretion from adrenocortical cells. Endocr Res. 2004;30(4):865–70.

41. Goodfriend TL, Ball DL, Raff H, Bruder ED, Gardner HW, Spiteller G. Oxidized products of linoleic acid stimulate adrenal steroidogenesis. Endocr Res. 2002;28(4):325–30.
42. de Haro MC, Figueiredo VN, de Faria AP, Barbaro NR, Sabbatini AR, Quinaglia T, et al. High-circulating leptin levels are associated with increased blood pressure in uncontrolled resistant hypertension. J Hum Hypertens. 2013;27(4):225–30. doi:10.1038/jhh.2012.29.
43.• Huby AC, Antonova G, Groenendyk J, Gomez-Sanchez CE, Bollag WB, Filosa JA, et al. The adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. Circulation. 2015. doi:10.1161/CIRCULATIONAHA.115.018226. **This report presents key information on the adipokine leptin is a direct regulator of aldosterone synthase (CYP11B2) expression and aldosterone release and promotes cardiovascular dysfunction via aldosterone-dependent mechanisms**.
44. Luo P, Dematteo A, Wang Z, Zhu L, Wang A, Kim HS, et al. Aldosterone deficiency prevents high-fat-feeding-induced hyperglycaemia and adipocyte dysfunction in mice. Diabetologia. 2013;56(4):901–10. doi:10.1007/s00125-012-2814-8.
45. Baudrand R, Pojoga LH, Romero JR, Williams GH. Aldosterone's mechanism of action: roles of lysine-specific demethylase 1, caveolin and striatin. Curr Opin Nephrol Hypertens. 2014;23(1):32–7. doi:10.1097/01.mnh.0000436543.48391.e0.
46. Shibata S, Fujita T. The kidneys and aldosterone/mineralocorticoid receptor system in salt-sensitive hypertension. Curr Hypertens Rep. 2011;13(2):109–15. doi:10.1007/s11906-010-0175-6.
47. Zennaro MC, Le Menuet D, Viengchareun S, Walker F, Ricquier D, Lombes M. Hibernoma development in transgenic mice identifies brown adipose tissue as a novel target of aldosterone action. J Clin Invest. 1998;101(6):1254–60. doi:10.1172/JCI1915.
48. Viengchareun S, Penfornis P, Zennaro MC, Lombes M. Mineralocorticoid and glucocorticoid receptors inhibit UCP expression and function in brown adipocytes. Am J Physiol Endocrinol Metab. 2001;280(4):E640–9.
49. Penfornis P, Viengchareun S, Le Menuet D, Cluzeaud F, Zennaro MC, Lombes M. The mineralocorticoid receptor mediates aldosterone-induced differentiation of T37i cells into brown adipocytes. Am J Physiol Endocrinol Metab. 2000;279(2):E386–94.
50. Caprio M, Feve B, Claes A, Viengchareun S, Lombes M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. FASEB J. 2007;21(9):2185–94. doi:10.1096/fj.06-7970com.
51. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab. 2007;92(3):1023–33. doi:10.1210/jc.2006-1055.
52. Bluher M. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes. 2012;19(5):341–6. doi:10.1097/MED.0b013e328357f0a3.
53. Kloting N, Fasshauer M, Dietrich A, Kovacs P, Schon MR, Kern M, et al. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab. 2010;299(3):E506–15. doi:10.1152/ajpendo.00586.2009.
54. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation. 2008;117(17):2253–61. doi:10.1161/CIRCULATIONAHA.107.748640.
55. Hirata A, Maeda N, Nakatsuji H, Hiuge-Shimizu A, Okada T, Funahashi T, et al. Contribution of glucocorticoid-mineralocorticoid receptor pathway on the obesity-related adipocyte dysfunction. Biochem Biophys Res Commun. 2012;419(2):182–7. doi:10.1016/j.bbrc.2012.01.139.
56. Boscaro M, Giacchetti G, Ronconi V. Visceral adipose tissue: emerging role of gluco- and mineralocorticoid hormones in the setting of cardiometabolic alterations. Ann N Y Acad Sci. 2012;1264:87–102. doi:10.1111/j.1749-6632.2012.06597.x.
57.• Armani A, Marzolla V, Fabbri A, Caprio M. Cellular mechanisms of MR regulation of adipose tissue physiology and pathophysiology. J Mol Endocrinol. 2015;55(2):R1–10. doi:10.1530/JME-15-0122. **This review summarizes the functions of cellular mechanisms of MR in the adipocyte, discusses potential signaling pathways mediating MR action, and describes post-translational modifications regulating its activity**.
58. Berger S, Bleich M, Schmid W, Greger R, Schutz G. Mineralocorticoid receptor knockout mice: lessons on Na+metabolism. Kidney Int. 2000;57(4):1295–8. doi:10.1046/j.1523-1755.2000.00965.x.
59. Bleich M, Warth R, Schmidt-Hieber M, Schulz-Baldes A, Hasselblatt P, Fisch D, et al. Rescue of the mineralocorticoid receptor knock-out mouse. Pflugers Arch - Eur J Physiol. 1999;438(3):245–54. doi:10.1007/s004240050906.
60. Lim HY, van den Brandt J, Fassnacht M, Allolio B, Herold MJ, Reichardt HM. Silencing of the mineralocorticoid receptor by ribonucleic acid interference in transgenic rats disrupts endocrine homeostasis. Mol Endocrinol. 2008;22(6):1304–11. doi:10.1210/me.2007-0417.
61. Ronzaud C, Loffing J, Bleich M, Gretz N, Grone HJ, Schutz G, et al. Impairment of sodium balance in mice deficient in renal principal cell mineralocorticoid receptor. J Am Soc Nephrol. 2007;18(6):1679–87. doi:10.1681/ASN.2006090975.
62. Ronzaud C, Loffing J, Gretz N, Schutz G, Berger S. Inducible renal principal cell-specific mineralocorticoid receptor gene inactivation in mice. Am J Physiol Renal Physiol. 2011;300(3):F756–60. doi:10.1152/ajprenal.00728.2009.
63. Grossmann C, Benesic A, Krug AW, Freudinger R, Mildenberger S, Gassner B, et al. Human mineralocorticoid receptor expression renders cells responsive for nongenotropic aldosterone actions. Mol Endocrinol. 2005;19(7):1697–710. doi:10.1210/me.2004-0469.
64. Dooley R, Harvey BJ, Thomas W. Non-genomic actions of aldosterone: from receptors and signals to membrane targets. Mol Cell Endocrinol. 2012;350(2):223–34. doi:10.1016/j.mce.2011.07.019.
65. Munoz-Durango N, Barake MF, Letelier NA, Campino C, Fardella CE, Kalergis AM. Immune system alterations by aldosterone during hypertension: from clinical observations to genomic and non-genomic mechanisms leading to vascular damage. Curr Mol Med. 2013;13(6):1035–46.
66. Yogi A, Callera GE, O'Connor S, Antunes TT, Valinsky W, Miquel P, et al. Aldosterone signaling through transient receptor potential melastatin 7 cation channel (TRPM7) and its alpha-kinase domain. Cell Signal. 2013;25(11):2163–75. doi:10.1016/j.cellsig.2013.07.002.
67. Gros R, Ding Q, Sklar LA, Prossnitz EE, Arterburn JB, Chorazyczewski J, et al. GPR30 expression is required for the mineralocorticoid receptor–independent rapid vascular effects of aldosterone. Hypertension. 2011;57(3):442–51. doi:10.1161/hypertensionaha.110.161653.
68. Caroccia B, Seccia TM, Campos AG, Gioco F, Kuppusamy M, Ceolotto G, et al. GPER-1 and estrogen receptor-beta ligands modulate aldosterone synthesis. Endocrinology. 2014;155(11):4296–304. doi:10.1210/en.2014-1416.

69. Sharma G, Hu C, Brigman JL, Zhu G, Hathaway HJ, Prossnitz ER. GPER deficiency in male mice results in insulin resistance, dyslipidemia, and a proinflammatory state. Endocrinology. 2013;154(11):4136–45. doi:10.1210/en.2013-1357.
70. Zhu P, Yuen JML, Sham KWY, Cheng CHK. GPER mediates the inhibitory actions of estrogen on adipogenesis in 3T3-L1 cells through perturbation of mitotic clonal expansion. Gen Comp Endocrinol. 2013;193:19–26. doi:10.1016/j.ygcen.2013.07.004.
71. Friso S, Carvajal CA, Fardella CE, Olivieri O. Epigenetics and arterial hypertension: the challenge of emerging evidence. Transl Res. 2015;165(1):154–65. doi:10.1016/j.trsl.2014.06.007.
72. Choi SW, Friso S. Epigenetics: a new bridge between nutrition and health. Adv Nutr. 2010;1(1):8–16. doi:10.3945/an.110.1004.
73.• Demura M, Demura Y, Takeda Y, Saijoh K. Dynamic regulation of the angiotensinogen gene by DNA methylation, which is influenced by various stimuli experienced in daily life. Hypertens Res. 2015;38(8):519–27. doi:10.1038/hr.2015.42. **This review highlights new evidences of epigenetic control of angiotensin gene (Agt) in adipose tissue. Agt gene, a RAAS gene, dynamically change its expression because exogenous and endogenous factors, as salt, glucocorticoids and mineralocorticoids in visceral adipose tissue**.
74. Wang F, Demura M, Cheng Y, Zhu A, Karashima S, Yoneda T, et al. Dynamic CCAAT/enhancer binding protein-associated changes of DNA methylation in the angiotensinogen gene. Hypertension. 2014;63(2):281–8. doi:10.1161/HYPERTENSIONAHA.113.02303.
75. Howard B, Wang Y, Xekouki P, Faucz FR, Jain M, Zhang L, et al. Integrated analysis of genome-wide methylation and gene expression shows epigenetic regulation of CYP11B2 in aldosteronomas. J Clin Endocrinol Metab. 2014;99(3):E536–43. doi:10.1210/jc.2013-3495.
76. Robertson S, MacKenzie SM, Alvarez-Madrazo S, Diver LA, Lin J, Stewart PM, et al. MicroRNA-24 is a novel regulator of aldosterone and cortisol production in the human adrenal cortex. Hypertension. 2013;62(3):572–8. doi:10.1161/HYPERTENSIONAHA.113.01102.
77. Sober S, Laan M, Annilo T. MicroRNAs miR-124 and miR-135a are potential regulators of the mineralocorticoid receptor gene (NR3C2) expression. Biochem Biophys Res Commun. 2010;391(1):727–32. doi:10.1016/j.bbrc.2009.11.128.
78. Kemp JR, Unal H, Desnoyer R, Yue H, Bhatnagar A, Karnik SS. Angiotensin II-regulated microRNA 483-3p directly targets multiple components of the renin-angiotensin system. J Mol Cell Cardiol. 2014;75:25–39. doi:10.1016/j.yjmcc.2014.06.008.
79. Misra M. Obesity pharmacotherapy: current perspectives and future directions. Curr Cardiol Rev. 2013;9(1):33–54.
80. Khorassani FE, Misher A, Garris S. Past and present of antiobesity agents: focus on monoamine modulators. Am J Health Syst Pharm. 2015;72(9):697–706. doi:10.2146/ajhp140034.
81. Costantino L, Barlocco D. New perspectives on the development of antiobesity drugs. Future Med Chem. 2015;7(3):315–36. doi:10.4155/fmc.14.167.
82. Gomez-Sanchez CE. What is the role of the adipocyte mineralocorticoid receptor in the metabolic syndrome? Hypertension. 2015;66(1):17–9. doi:10.1161/HYPERTENSIONAHA.115.05148.
83. Jing F, Mogi M, Horiuchi M. Role of renin–angiotensin–aldosterone system in adipose tissue dysfunction. Mol Cell Endocrinol. 2013;378(1–2):23–8. doi:10.1016/j.mce.2012.03.005.
84. Brown NJ. This is not Dr. Conn's aldosterone anymore. Trans Am Clin Climatol Assoc. 2011;122:229–43.
85. Fontana V, de Faria AP, Oliveira-Paula GH, Silva PS, Biagi C, Tanus-Santos JE, et al. Effects of angiotensin-converting enzyme inhibition on leptin and adiponectin levels in essential hypertension. Basic Clin Pharmacol Toxicol. 2014;114(6):472–5. doi:10.1111/bcpt.12195.
86. Nedogoda SV, Ledyaeva AA, Chumachok EV, Tsoma VV, Mazina G, Salasyuk AS, et al. Randomized trial of perindopril, enalapril, losartan and telmisartan in overweight or obese patients with hypertension. Clin Drug Investig. 2013;33(8):553–61. doi:10.1007/s40261-013-0094-9.
87. Sarzani R, Guerra F, Mancinelli L, Buglioni A, Franchi E, Dessi-Fulgheri P. Plasma aldosterone is increased in class 2 and 3 obese essential hypertensive patients despite drug treatment. Am J Hypertens. 2012;25(7):818–26. doi:10.1038/ajh.2012.47.
88. Schrier RW. Aldosterone 'escape' vs 'breakthrough'. Nat Rev Nephrol. 2010;6(2):61. doi:10.1038/nrneph.2009.228.
89. Marcus Y, Shefer G, Sasson K, Kohen F, Limor R, Pappo O, et al. Angiotensin 1–7 as means to prevent the metabolic syndrome: lessons from the fructose-fed rat model. Diabetes. 2013;62(4):1121–30. doi:10.2337/db12-0792.
90. Schuchard J, Winkler M, Stölting I, Schuster F, Vogt FM, Barkhausen J, et al. Lack of weight gain after angiotensin AT1 receptor blockade in diet-induced obesity is partly mediated by an angiotensin-(1–7)/Mas-dependent pathway. Br J Pharmacol. 2015;172(15):3764–78. doi:10.1111/bph.13172.
91.• Azizi M, Amar L, Menard J. Aldosterone synthase inhibition in humans. Nephrol Dial Transplant. 2013;28(1):36–43. doi:10.1093/ndt/gfs388. **This review summarizes recent in vitro and preclinical studies of CYP11B2 inhibitors, hormonal and haemodynamic effects, and highlights potential side-effects as a class**.
92. Papillon JPN, Lou C, Singh AK, Adams CM, Ksander GM, Beil ME, et al. Discovery of N-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide, a cortisol-sparing CYP11B2 inhibitor that lowers aldosterone in human subjects. J Med Chem. 2015. doi:10.1021/acs.jmedchem.5b01545.
93.• Strushkevich N, Gilep AA, Shen L, Arrowsmith CH, Edwards AM, Usanov SA, et al. Structural insights into aldosterone synthase substrate specificity and targeted inhibition. Mol Endocrinol. 2013;27(2):315–24. doi:10.1210/me.2012-1287. **This paper reports the crystal structures of human aldosterone synthase in complex with a substrate deoxycorticosterone and an first generation CYP11B2 inhibitor fadrozole**.
94. Cerny MA, Csengery A, Schmenk J, Frederick K. Development of CYP11B1 and CYP11B2 assays utilizing homogenates of adrenal glands: utility of monkey as a surrogate for human. J Steroid Biochem Mol Biol. 2015;154:197–205. doi:10.1016/j.jsbmb.2015.08.004.
95. Armani A, Cinti F, Marzolla V, Morgan J, Cranston GA, Antelmi A, et al. Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. FASEB J. 2014;28(8):3745–57. doi:10.1096/fj.13-245415.
96.•• Garg R, Kneen L, Williams GH, Adler GK. Effect of mineralocorticoid receptor antagonist on insulin resistance and endothelial function in obese subjects. Diabetes Obes Metab. 2014;16(3):268–72. doi:10.1111/dom.12224. **This paper reports the results of the single clinical study of MR antagonists for the treatment of obesity, However only non-diabetic healthy obese were included in the study**.
97. Peelman F, Zabeau L, Moharana K, Savvides SN, Tavernier J. 20 years of leptin: insights into signaling assemblies of the leptin receptor. J Endocrinol. 2014;223(1):T9–23. doi:10.1530/joe-14-0264.
98. Gertler A, Solomon G. Leptin-activity blockers: development and potential use in experimental biology and medicine. Can J Physiol Pharmacol. 2013;91(11):873–82. doi:10.1139/cjpp-2013-0012.

99. Okada-Iwabu M, Iwabu M, Ueki K, Yamauchi T, Kadowaki T. Perspective of small-molecule adipoR agonist for type 2 diabetes and short life in obesity. Diabetes Metab J. 2015;39(5):363–72. doi:10.4093/dmj.2015.39.5.363.

100. Lim S, Quon MJ, Koh KK. Modulation of adiponectin as a potential therapeutic strategy. Atherosclerosis. 2014;233(2):721–8. doi:10.1016/j.atherosclerosis.2014.01.051.

101.• Tanabe H, Fujii Y, Okada-Iwabu M, Iwabu M, Nakamura Y, Hosaka T, et al. Crystal structures of the human adiponectin receptors. Nature. 2015;520(7547):312–6. doi:10.1038/nature14301. **This paper reports the crystal structures of human AdipoR1 and AdipoR2, a novel class of receptor structures, with a seven-transmembrane helices arrangement, conformationally distinct from those of G-protein-coupled receptors**.