Obesity, hypertension and aldosterone: is leptin the link?

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Abstract

Obesity is a serious health hazard with rapidly increasing prevalence in the United States. In 2014, the World Health Organization estimated that nearly 2 billion people worldwide were overweight with an estimated 600 million of these obese. Obesity is associated with many chronic diseases, including cardiovascular disease and hypertension. Data from the Framingham Heart study suggest that approximately 78% of the risk for hypertension in men and 65% in women is related to excess body weight, a relationship that is further supported by studies showing increases in blood pressure with weight gain and decreases with weight loss. However, the exact mechanism by which excess body fat induces hypertension remains poorly understood. Several clinical studies have demonstrated elevated plasma aldosterone levels in obese individuals, especially those with visceral adiposity, with decreased aldosterone levels measured in concert with reduced blood pressure following weight loss. Since aldosterone is a mineralocorticoid hormone that regulates blood volume and pressure, serum aldosterone levels may link obesity and hypertension. Nevertheless, the mechanism by which obesity induces aldosterone production is unclear. A recent study by Belin de Chantemele and coworkers suggests that one adipose-released factor, leptin, is a direct agonist for aldosterone secretion; other adipose-related factors may also contribute to elevated aldosterone levels in obesity, such as very low-density lipoprotein (VLDL), the levels of which are elevated in obesity and which also directly stimulates aldosterone biosynthesis. This focused review explores the possible roles of leptin and VLDL in modulating aldosterone secretion to underlie obesity-associated hypertension.

Key Words
▶ adipose tissue
▶ aldosterone
▶ hypertension
▶ leptin
▶ obesity

It is well known that obesity is associated with a number of metabolic end organ dysfunctions, including hypertension. However, less well understood is the mechanism by which obesity leads to elevated blood pressure. Various hypotheses have been proposed including increased sympathetic nervous system activity, overactivation of the renin-angiotensin II-aldosterone system, excessive secretion of adipose-derived cytokines, inflammation and compression of the kidneys by excess perirenal fat deposits (Canale *et al.* 2013). On the other hand, accumulating evidence suggests a potential link between obesity-related hypertension and the

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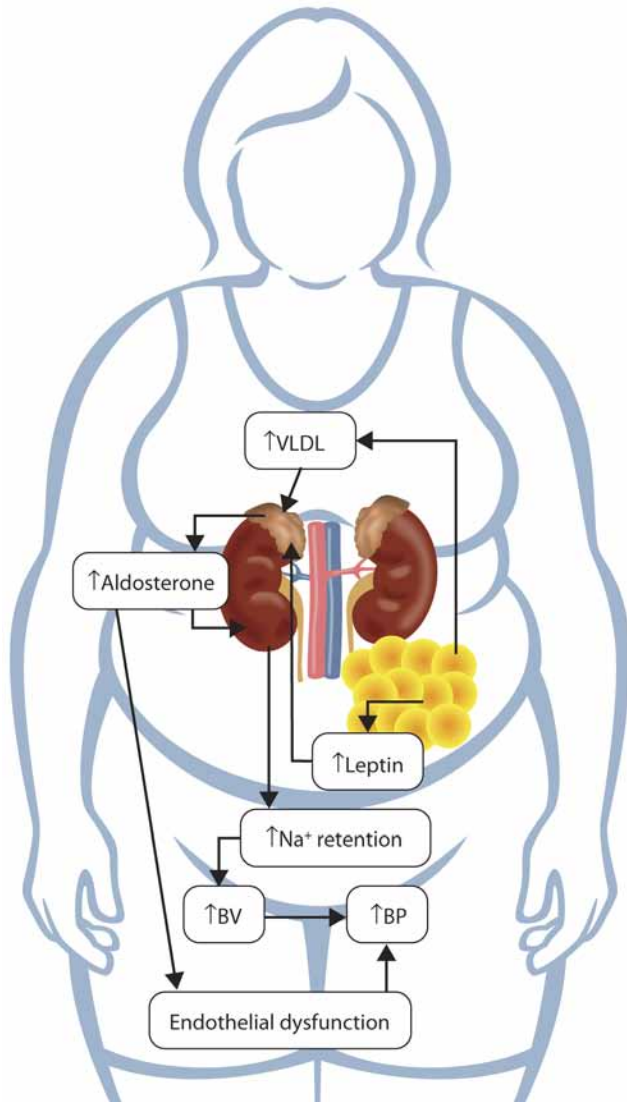
Figure 1

Obesity increases blood pressure. Excess fat deposits (including those surrounding the adrenal glands) of obese individuals secrete large amounts of leptin. The data of Belin de Chantemele and coworkers indicate that this adipose-derived leptin can stimulate zona glomerulosa cells of the adrenal gland to produce aldosterone. Aldosterone, in turn, causes the kidney to retain salt and water, raising blood volume and pressure. Aldosterone can also produce endothelial dysfunction and cardiac fibrosis. Obesity also results in dyslipidemia, including increased serum levels of VLDL; this lipoprotein has also been shown to induce aldosterone production. Other mechanisms (not illustrated) that potentially underlie obesity-associated hypertension include increased levels of proinflammatory cytokines, hypersecretion of various adipokines and/or excessive activity of the sympathetic nervous or renin-angiotensin II-aldosterone systems.

mineralocorticoid aldosterone (Briet & Schiffrin 2011), a steroid hormone involved in maintaining fluid and electrolyte balance in the human body. Thus, aldosterone

levels are elevated in obesity, and weight loss in obese individuals is accompanied by reductions in both blood pressure and aldosterone levels (Calhoun & Sharma 2010, Briet & Schiffrin 2011). Furthermore, in several studies, aldosterone levels have been correlated with body mass index, waist circumference and/or visceral adiposity (Calhoun & Sharma 2010). Based on this link between obesity and aldosterone levels, it has been proposed that adipose tissue produces a factor or factors that can stimulate aldosterone secretion from the adrenal gland independently of the traditional aldosterone secretagogues, angiotensin II (AngII), elevated serum potassium levels and adrenocorticotrophic hormone (ACTH). Nevertheless, the identity of this adipose-secreted factor is unclear.

Since the discovery of leptin as an adipocyte-derived satiety factor, adipose tissue is no longer viewed simply as a passive energy storage site but also as an active endocrine and paracrine organ secreting an ever-increasing number of mediators, termed adipokines. Research indicates that adipocytes communicate with other organs through these adipokines and participate in diverse metabolic processes including cardiovascular function (Rondinone 2006). Leptin, a protein hormone secreted predominantly by adipocytes in proportion to fat mass, plays a role in the regulation of food intake and a series of other physiologic actions, including blood pressure control, through its widely distributed receptors (Rondinone 2006). It has been previously demonstrated that leptin receptors are expressed in human and rat adrenal glomerulosa cells (Ehrhart-Bornstein *et al.* 2003), although available data on the direct effects of leptin on aldosterone secretion *in vitro* are controversial (e.g., Malendowicz *et al.* 1997 vs Salzmann *et al.* 2004). Nevertheless, obesity is characterized by concomitant hyperleptinemia and hyperaldosteronism, and decreases in both aldosterone and leptin are observed with weight reduction, suggesting a possible interaction of these two hormones (Engeli & Sharma 2000). Indeed, a recent article from the laboratory of Belin de Chantemele (Huby *et al.* 2015) provides strong evidence, both *in vitro* and *in vivo*, that the adipokine leptin is an important aldosterone stimulatory factor released from adipose tissue (Fig. 1).

In this article, Huby and coworkers (2015) first demonstrated that leptin receptors can be localized to aldosterone synthase (CYP11B2)-positive zona glomerulosa cells in human adrenal glands, and are present in isolated rat adrenocortical cells and the human adrenocortical carcinoma cell line, HAC15 cells. Leptin

also dose-dependently increases aldosterone production and CYP11B2 protein levels in HAC15 adrenocortical carcinoma cells and rat adrenocortical cells *in vitro* in a leptin receptor-dependent manner. Leptin induces an increased cytosolic calcium concentration that is required for the observed changes in aldosterone and CYP11B2 levels. In addition, infusion of leptin in wild-type or ob/ob female mice lacking leptin *in vivo* results in a dose-dependent increase in serum aldosterone levels and aldosterone synthase protein expression without affecting serum sodium, potassium, AngII or ACTH levels. These elevations are inhibited by a leptin receptor antagonist, but not AngII type 1 (AT1R) or adrenergic receptor antagonists, and leptin infusion into db/db mice with nonfunctional leptin receptors does not produce such effects. Interestingly, while the ability of leptin to inhibit food intake becomes desensitized with continued hormone infusion, the effect of leptin to stimulate aldosterone secretion does not. Additional mouse models in which leptin or leptin signaling is enhanced also exhibit increased aldosterone and CYP11B2 protein levels: thus, these parameters are elevated in protein tyrosine phosphatase knockout mice, in which inactivation of leptin signaling is inhibited, in obese agouti mice with enhanced leptin levels and in high-fat-diet-induced obese mice, which also show higher leptin levels. Finally, leptin infusion into mice *in vivo* results in endothelial dysfunction and cardiac fibrosis, both of which can be reversed with the mineralocorticoid receptor (MR) antagonist spironolactone, suggesting that certain adverse effects of elevated leptin levels accompanying obesity may be attributable to this hormone's ability to increase aldosterone levels.

This study, which utilizes multiple *in vivo* rodent models as well as *in vitro* adrenocortical cell systems, strongly supports the idea that leptin is an adipose-derived factor that can directly promote aldosterone secretion. However, the experiments reported in this article were performed in female rodents; this group subsequently demonstrated that the aldosterone stimulatory effect of leptin underlies obesity-associated hypertension only in female mice, but not in males, in which leptin seems to exert its hypertensive effect instead through activation of the sympathetic nervous system (Huby *et al*. 2016). These data also seem to be consistent with results in humans, in that, for example, women exhibit a greater response to MR antagonists than men (Goodfriend *et al*. 1999). Nevertheless, despite the demonstrated, but possibly gender-specific, role of leptin in elevating aldosterone levels, it seems likely that leptin is not the only adipokine that regulates aldosterone

production in the zona glomerulosa to contribute to obesity-associated hypertension.

Other cytokines released by adipose tissue, such as tumor necrosis factor-α, interleukin-6, complement-C1q TNF-related protein 1 (CTRP1) and fatty acid oxidation products (Briet & Schiffrin 2011), as well as additional factors known to be augmented in obesity, may also lead to elevated blood pressure through stimulated aldosterone secretion. For example, obesity is often associated with dyslipidemia, characterized by increased circulating plasma triglycerides, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) levels (Briet & Schiffrin 2011). This atherogenic dyslipidemia is an important contributor to the deleterious effects of being overweight or obese. VLDL has high triglyceride content (about 50%) and serves to transport this lipid in the body; however, previous studies have shown that in addition to transporting lipids, VLDL can regulate signaling pathways in different tissue types. For example, VLDL modulates the expression in human endothelial cells of a variety of genes involved in, for example, cell signaling, cell transport and extracellular matrix formation and degradation (Norata *et al*. 2003). Oxidized VLDL regulates the expression of some of the same genes, but VLDL and oxidized VLDL each also alter the expression of their own set of genes, through activation of primarily extracellular signal-regulated kinase-1 and -2 (ERK1/2) in the case of VLDL and predominantly p38 mitogen-activated kinase with oxidized VLDL (Norata *et al*. 2003). These results, and others, indicate that VLDL can activate cell signaling pathways in various cell types in addition to transporting lipids throughout the body.

In recent studies, we showed in primary cultures of human adrenocortical and bovine glomerulosa cells, as well as the adrenocortical cell line, H295R, and its clone the HAC15 cell line, that VLDL significantly increases aldosterone synthesis in these various models of zona glomerulosa cells (Xing *et al*. 2012, Tsai *et al*. 2014). This stimulation occurs at physiological VLDL levels of 30–100 μg protein/mL and is largely due to VLDL's stimulation of the expression of steroidogenic acute regulatory protein and CYP11B2 (Xing *et al*. 2012). In the H295R cell line, the effects of VLDL on CYP11B2 transcript levels are not additive with high AngII or elevated extracellular potassium levels, but are additive with the cAMP-elevating agents ACTH and forskolin (Xing *et al*. 2012) and are not altered by exposure to an AT1R antagonist (Tsai *et al*. 2014). The effect of VLDL on aldosterone and CYP11B2 involves the calcium signaling pathway, as the changes can be inhibited by antagonists

of voltage-dependent L-type calcium channels and calcium/calmodulin-dependent protein kinases (Xing *et al.* 2012). Phospholipase D has also been found to mediate aldosterone production and CYP11B2 expression in response to VLDL (Tsai *et al.* 2014), similarly to its role in AngII-induced steroidogenesis. Finally, we also showed that rats on a chow and liquid-sucrose diet that induces obesity and insulin resistance exhibit increased aldosterone synthase levels correlating with elevated triglyceride levels (a measure of VLDL levels in fasted animals) *in vivo* (Xing *et al.* 2012).

These results are similar to the data of Saha and coworkers, who showed that VLDL and oxidized VLDL stimulate aldosterone production. *In vitro* glycoxidized VLDL, which increases in diabetes (Saha *et al.* 2012*b*), also induces steroidogenesis (Saha *et al.* 2012*a,b*); VLDL prepared from individuals with impaired glucose tolerance stimulates aldosterone secretion as well (Saha *et al.* 2013). Using pharmacologic inhibitors, these authors also demonstrated that the effects of modified and unmodified VLDL are mediated by cAMP-dependent protein kinase, ERK1/2 and Janus kinase-2 through scavenger receptor class B, member 1 (Saha *et al.* 2012*a*). High-density lipoprotein also increases aldosterone production (Xing *et al.* 2011, Saha *et al.* 2012*b*), although its effects are less robust and more variable (Xing *et al.* 2012, Saha *et al.* 2012*b*). On the other hand, while some investigators have detected a steroidogenic effect of LDL (Saha *et al.* 2012*b*), the ability of this lipoprotein to stimulate aldosterone production remains controversial (Capponi 2002). Nevertheless, these data suggest the possibility that obesity-altered lipoproteins can also promote aldosterone production to contribute to hypertension.

Obesity-induced hypertension should be considered the most common form of essential hypertension. Indeed, data from the Framingham Heart Study suggest that about 78% of the risk for hypertension in men and approximately 65% in women can be directly related to excess body weight (Calhoun & Sharma 2010). This relationship has been further supported by experimental studies showing an increase in blood pressure after weight gain, as well as the therapeutic value of weight loss in reducing blood pressure (Kawarazaki & Fujita 2016). Additional data from the Framingham Offspring Study indicate that high levels of plasma aldosterone, albeit in the normal range, predict the development of hypertension (Garrison *et al.* 1987). In addition to hypertension, aldosterone is thought to mediate various other processes that contribute to cardiorenal disease, such as cardiac fibrosis, proteinuria

and endothelial dysfunction, through its interaction with and activation of MR (Calhoun & Sharma 2010). On the other hand, the glucocorticoid cortisol, perhaps acting through the MR, has also been proposed to contribute to obesity-associated hypertension (Varughese *et al.* 2014). Indeed, excess cortisol in Cushing's syndrome is associated with symptoms of metabolic syndrome, including abdominal obesity and hypertension. In many tissues, cortisol, which has the same affinity for the MR as aldosterone, is prevented from activating MR by the action of 11β-hydroxysteroid dehydrogenase-2 (11βHSD2), which converts cortisol to its inactive metabolite, cortisone. Cortisone, in turn, can be reactivated by the enzyme 11β-hydroxysteroid dehydrogenase-1 (11βHSD1), and it has been proposed that excess cortisol, either in the serum or produced locally by dysregulation of 11βHSD1 and/or 11βHSD2, may be able to activate MR to contribute to obesity-associated hypertension (Varughese *et al.* 2014). Thus, multiple mechanisms may operate to mediate the hypertension linked to obesity. These additional mediators may explain the fact that not all studies have shown a correlation between adipose depots and aldosterone levels (e.g. O'Seaghdha *et al.* 2012) and/or between BMI and the response to an MR antagonist (Chapman *et al.* 2007, for example). Additional factors that may play a role in the observed heterogeneity of the data resulting from human studies include the proportion of male to female subjects (if as in mice (Huby *et al.* 2016), aldosterone contributes to a greater extent to obesity-associated hypertension in females (Goodfriend *et al.* 1999)), the absolute BMI of the subjects (i.e., normal weight versus overweight versus obese) and the relative adipose tissue distribution (e.g., visceral versus subcutaneous fat), as well as perhaps other parameters that have not yet been determined. Nevertheless, the results presented by Huby and coworkers (Huby *et al.* 2015), demonstrating that adipocyte-derived leptin likely mediates, at least in part, the effect of obesity on blood pressure by modulating aldosterone secretion, indicate that further studies are warranted.

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