

Role of adipocytes in hypertension

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Abstract

Although it has known for some time that obesity is associated with salt sensitivity and hypertension, recent data suggests that the adipocyte may actually be the proximate cause of this physiological changes. In the following review, the data demonstrating this association as well as the potentially operative pathophysiological

mechanisms are reviewed and discussed.

Key words: Hypertension; Oxidant stress; Natriuresis; Heme oxygenase; Nitric oxide; Renal function; Obesity

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Core tip: Hypertension is a growing problem worldwide, and the problem is exacerbated by the growing obesity epidemic. This review looks into the complex relationship between these two diseases, outlining what current literature reports for treatment methods, hypotheses on cause, and potential cross talk between the two.

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INTRODUCTION

Hypertension is defined as elevated blood pressure—typically a systolic blood pressure of ≥ 140 mmHg or a diastolic pressure ≥ 90 mmHg (or both) in a relaxed state^[1-3]. Currently, 29% (or 70 million) of Americans have been diagnosed with hypertension^[4,5]. There are several stages of hypertension, as well as salt sensitive and salt resistant types of hypertension^[6]. Hypertension may complicate and/or worsen other diseases such as diabetes, cardiovascular disease, chronic kidney disease, and obesity^[2,7-9]. Obesity itself has reached pandemic proportions; according to the World Health Organization (WHO), over 500 million adults (10%-14% of world population) were obese in 2008, and this number keeps increasing^[2,8,9]. As of 2014, this number has jumped to 600 million. There is an association between hypertension and obesity, but the mechanism(s) by which obesity predisposes to hypertension in humans

has not been clearly established. In this review, we will explore some aspects of this important relationship.

THE THREE KNOWN TYPES OF ADIPOSE TISSUE

Currently there are three known types of adipose tissue, each with its own specific characteristics: White, brown, and a mixture type, known as beige (or "brite"). The main purpose of adipose, regardless of the type, is to store excess energy that can be released as needed. The way the energy is stored varies between types. White adipose is the type one would think about when thinking about typical obesity. White adipocytes (WAT) are characterized by a spherical shape, a large lipid droplet that takes up 90% of the volume of the cell, very few mitochondria, and a flattened peripheral nucleus^[10-15]. WAT can release triglycerides during a time of energy crisis in the body. WAT can be found virtually anywhere on the body, but are mainly located in subcutaneous abdomen, viscera, retroperitoneal, inguinal, and gonadal areas^[10,16-19]. White adipocyte cells are known to secrete several kinds of proteins, such as inflammatory factors and the protein leptin^[18-23].

Leptin is known as the satiety protein; when released, it inhibits feelings of hunger^[13,14]. The antagonist of leptin is ghrelin; this is thought to be one of the hunger hormones^[13,18,19,23]. It has clearly been shown by Sennello *et al.*^[24] and Friedman *et al.*^[25-27] that patients with an inability to produce leptin develop profound hyperphagia and obesity. However, in most obese subjects, leptin levels are high^[25,26]. In these subjects, it is thought that as leptin levels are chronically elevated, responses to leptin are diminished^[25]. Despite the high amount of energy already stored, the body ignores satiety signals and thinks it requires more energy to store; this higher level of leptin is consistent with a higher amount of adipocytes which are believed to be the primary source of leptin^[25,26,28,29]. This hormone and protein releasing function therefore places white adipose tissue as an endocrine organ^[14,30,31].

In addition to leptin, adipocytes also release other hormones and peptides, including tumor necrosis factor α (TNF α) and interleukin-6 (IL-6)^[32-35]. These are inflammatory cytokines, and the increased levels are indicative of inflammation in the body^[32-34]. Whether this inflammation leads to increased reactive oxygen species (ROS) production creating oxidative stress or oxidative stress from signaling leads to inflammation is currently unclear.

Brown adipocytes (BAT) are a bit different from WAT; they are polygonal in shape, contain fewer and smaller lipid molecules, have abundant mitochondria, and a central round nuclei^[10,11,36]. BAT are mainly found in the subscapular region of rodents and human infants^[10,37]. Whereas WAT use lipids to store energy, BAT store energy in the form of fat and break them down to produce heat in a process known as non-shivering thermogenesis^[38-40].

Thermogenesis is the production of heat in an organism; non-shivering thermogenesis occurs in the brown adipose tissue because of the presence of thermogenin^[41-44]. Thermogenin (also known as uncoupling protein 1) allows the uncoupling of protons moving down their gradient from adenosine triphosphate (ATP) synthesis; this energy is then dissipated as heat^[43,44]. Free fatty acids from the brown adipose tissue remove any proteins that could inhibit thermogenin^[41,42]. Thermogenin then causes an influx of H⁺ into the mitochondrial matrix, bypassing the ATP synthase normally used to make ATP^[45-49]. This uncouples oxidative phosphorylation, and the energy normally used to convert adenosine diphosphate (ADP) to ATP is released as heat^[46,50-52]. Interestingly, thermogenesis can also be produced by ion pump leakage^[50,53,54]. It is thought that a leaky ion pump in mitochondria releases H⁺ ions; the intensity of heat is proportional to the amount of H⁺ released during this process^[41,43]. The ability of BAT to turn excess energy into heat is a property the WAT lack^[4,55-57]. Circulating factors, such as irisin, FGF-21, and natriuretic peptides play a role in regulating BAT^[4,55-57]. It is thought that these factors can encourage proliferation of BAT, and increase the amount of present beige adipocytes^[55,56,58].

Beige adipocytes are a combination of brown and WAT^[4]. Beige adipocytes are born through a browning process; WAT become more like BAT, the one large lipid droplet becomes many, and uncoupling protein 1 becomes expressed, and thermogenic activity increases^[5,56,58]. All three types of adipocyte cells, along with muscle cells, come from the same precursor cell—a mesenchymal stem cell^[4,5]. The expression of different genes at different points during the life cycle of these cells determines their fate^[4,5], see Figure 1. The potential for obese adults to spontaneously form beige adipocytes from their WAT is unclear, but it brings to mind the possibility that such a phenomenon is possible.

THE RELATIONSHIP BETWEEN HYPERTENSION AND OBESITY

Obesity can increase the susceptibility to metabolic syndromes, cardiovascular diseases, type 2 diabetes, cancer, and hypertension^[2,7-9]. Although some patients with hypertension are not obese, and *vice versa*, there is a strong correlation across populations^[59]. The interactions between obesity, salt sensitivity and hypertension are shown schematically in Figure 2. When blood pressures reach the hypertensive range, there is almost always small vessel disease of the arterioles, or arteriolosclerosis, as well as kidney damage^[60-62]. This strongly suggests that there are both vascular and renal components to the disease^[63]. Hypertension has genetic and environmental factors in addition to those associated with obesity^[4,29,64,65]. Salt sensitive hypertension refers to an increase in blood pressure related to an increase in salt (specifically sodium) intake^[6,66,67]. Some workers in this field believe that all hypertension reflects either excessive sodium intake or

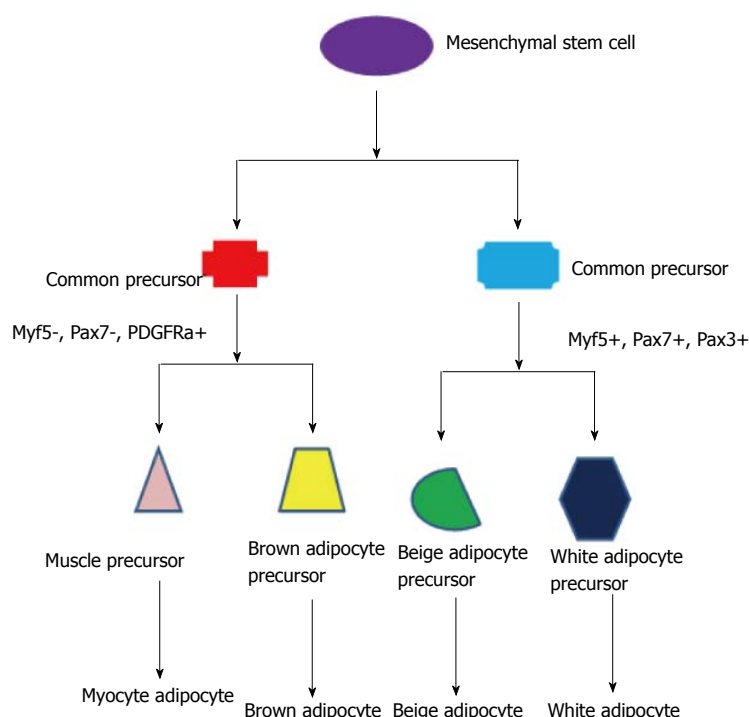


Figure 1 Schematic demonstrating links between three basic type of adipocytes and muscle. All cells come from the same common cell, mesenchymal stem cell. Presence or absence of certain factors during development, such as Myf5, Pax 3 and 7, PDGFRa and myogenin can affect the final product of the cell. Myf5: Myogenic factor 5; Pax 7: Paired box protein 7; Pax 3: Paired box protein 3; PDGFRa: Platelet-derived growth factor receptor, alpha polypeptide.

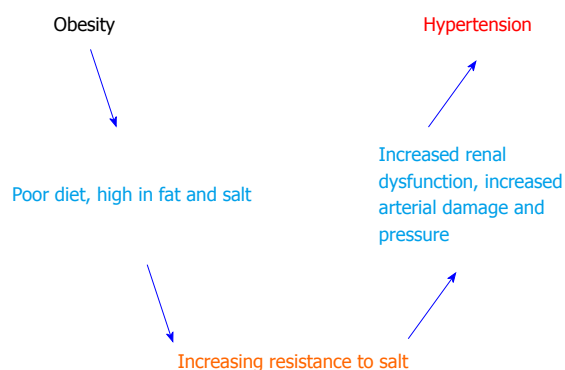


Figure 2 Schematic demonstrating potential relationship between obesity and hypertension.

some form of renal salt sensitivity, but this is admittedly still controversial^[63,68-70].

PRESENT THEORIES LINKING OBESITY TO HYPERTENSION

Obesity appears to be associated with or complicated by "increased sympathetic nervous system (SNS) activity, activation of the renin-angiotensin aldosterone system (RAAS), and physical compression of the kidneys by extra-renal fat and by increased intrarenal extracellular matrix"^[71-73]. This physical compression can directly activate the RAAS which, in turn, leads to increased SNS outflow as well as increased circulating concentrations of angiotensin II, a well-known vasoconstrictor and aldosterone, an anti-natriuretic hormone. The net effect is sodium retention and increased blood pressure^[63,73-75]. Leptin levels, as discussed above, appear to be increased in obese patients. This hormone through several biochemical mechanisms,

affects appetite as well as SNS outflow, and can cause increases in blood pressure^[71,74]. The duration of obesity also plays a role; the longer one is obese, the more renal damage occurs which further impairs pressure natriuresis, exacerbating hypertension^[63,71,72,76,77].

Another potentially contributing factor is obstructive sleep apnea (OSA), which is more than just another co-morbidity of obesity. OSA is much more common in people who are overweight or obese^[1,2]. OSA occurs when the airway becomes blocked or constricted and can cause snoring, and lapses in breathing that are common to sleep apnea^[2,78,79]. Untreated sleep apnea can lead to increases in blood pressure, obesity, heart attack risk, and diabetes, among other problems^[2,7,75,80-82]. In addition to increasing the risk for hypertension, OSA can lead to other problems. Hypoxia, or lack of oxygen that occurs when breathing is stopped or obstructed, is also a risk factor for generating ROS and increasing oxidant stress and SNS activity^[1,2,78,82].

Recent work suggests that the adipocyte itself could play an important role in hypertension. Research has shown that high dietary sodium can increase the white adipocyte mass as well as leptin levels in rats^[82], and blood pressure was significantly increased as well. The increase in adipocyte mass has a cascading effect; the mass increases, the release of additional adipokines occurs, and these lead to an increase in inflammation. This inflammation causes further exacerbation of disordered metabolism and insulin resistance^[82-85]. These interactions are shown schematically in Figures 3 and 4.

CURRENT TREATMENTS OF OBESITY AND THEIR EFFECTS ON HYPERTENSION

Currently, there are several treatment methods to deal with

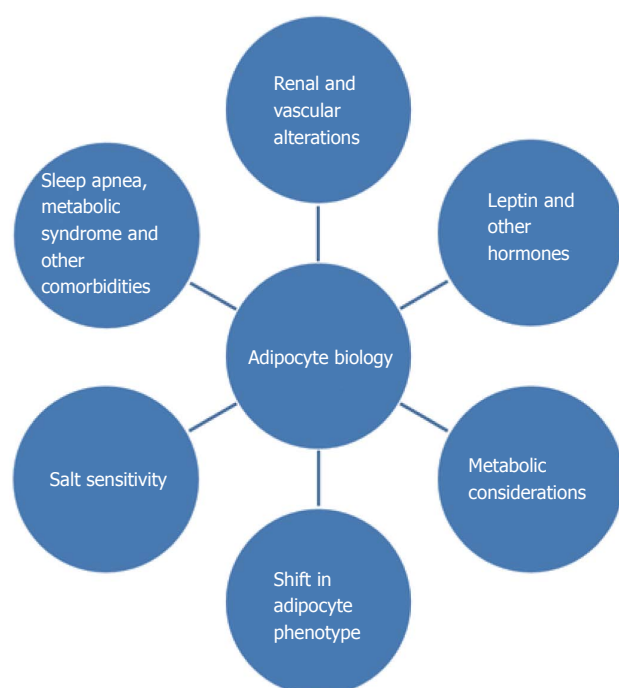


Figure 3 Visual representation of factors contributing to the complex pathophysiology linking adipocyte biology and hypertension.

obesity, and as it is so closely related with hypertension, treatments for the two can often overlap^[86-88]. The treatments can be broken up into several categories; lifestyle changes (including nutritional changes and exercise addition), drug therapy, and surgical methods^[89]. It has been shown that a reduction in a patient's weight by 5%-10% is enough to reduce their risk of cardiovascular complications, including hypertension^[89-91]. When looking at the drug treatment route, it is important to consider however that some drugs are not recommended for patients who have pre-existing conditions, such as hypertension or diabetes. Sibutramine, for example, has been associated with small increases in blood pressure and heart rate, and is not recommended for patients suffering from hypertension^[89,92]. Some drugs that are used to treat hypertension can be used as a weight loss agent, such as the drug orlistat^[89,93]. These drugs can work on multiple levels; some are known as feeder modulators, and change the way the patient receives signals that the body needs food^[89,94]. Some effect the formation of agents such as angiotensin II and nitric oxide synthase (NOS)^[89,95,96]. Still others work at the molecular level and effect the afferent signaling that can lead to obesity^[89,95]. Serotonin drugs have been found to be an effective treatment of obesity, but the downside is they can cause an increased risk of primary hypertension because of their effects on vascular smooth muscle^[97]. If we look at surgical approaches, the benefits of surgery on hypertension itself and the abnormal hormonal milieu appear to be huge, at least over the first year or so^[98].

REDOX REACTIONS AND THEIR RELATION TO OBESITY AND HYPERTENSION

In addition to salt intake and obesity, nitrous oxide synthase and heme oxygenase (HO) both play a role in the cause and treatment of hypertension^[99-101]. Obesity leads to an imbalance in the circulating level of nitric oxide (NO); this is due to increased oxidative stress and decreased NO production^[100,102]. Decreasing the availability of the NO can predispose an individual to hypertension^[99-101]. NO contributes to vasodilation, which is the relaxation of the vasculature^[83,99-101]. If there is less NO present (because of a decrease in NO synthase), vasoconstriction can occur, which can exacerbate the damage of increased pressure from the other factors related to hypertension^[99-101]. Human adipose tissue expresses angiotensinogen, angiotensin-converting enzyme (ACE) as well as angiotensin type 1 (AT1), and AT2 receptors^[102-105]. The role of angiotensin is not well known, but it has some kind of redox purpose; it appears to involve inhibition of endothelial cell migration, proliferation and induction of apoptosis^[65,99-101]. There is a link between NO synthase dysfunction and the ACE enzyme in the obese population^[99-101]. Excessive NO formation by the inducible member of the NOS family (iNOS or Nos2) has been shown to cause nonspecific tissue damage; it is thought to be involved in the pathogenesis of inflammatory and autoimmune diseases^[106-108]. By inhibiting this inducible factor, obesity still occurs but the pathologies associated are reduced^[107]. A similar study showed that even though mice protected from pathologies associated with iNOS inhibition, they are still subjected to increased blood pressure and increased ROS^[109,110]. iNOS is associated with increased inflammatory responses, which is related to the cascade of responses associated with obesity and hypertension^[33,34,111,112]. It is known that increased NO can induce cellular stress, which can exacerbate the current problems present.

Similarly to NO synthase, HO has a role in amelioration of hypertension^[1,100,104,107,113]. An increase in HO expression can cause reductions in ROS, or ROS. Increases in ROS, also called oxidant stress, are believed to be important in the progression of hypertension and associated cardiovascular diseases^[65,81,87,93]. The isoform HO-1 is the inducible form of HO, and when induced it can cause a decrease in weight, and therefore a decrease in obesity^[113-115]. HO does this by changing the phenotype of the adipocyte^[113,116]. HO-1 can interact with NO in several ways, one of which is through Ang II^[99,117,118]. Increased Ang II production causes an increase in ROS, which may inhibit the action of NO^[100,119]. This can also increase salt reabsorption. When HO-1 expression is increased, the increases in Ang II levels are attenuated; this decreases Ang II's downstream signaling effects^[99,117,118]. Induction of HO-1 can also reduce the renal vasculature resistance that

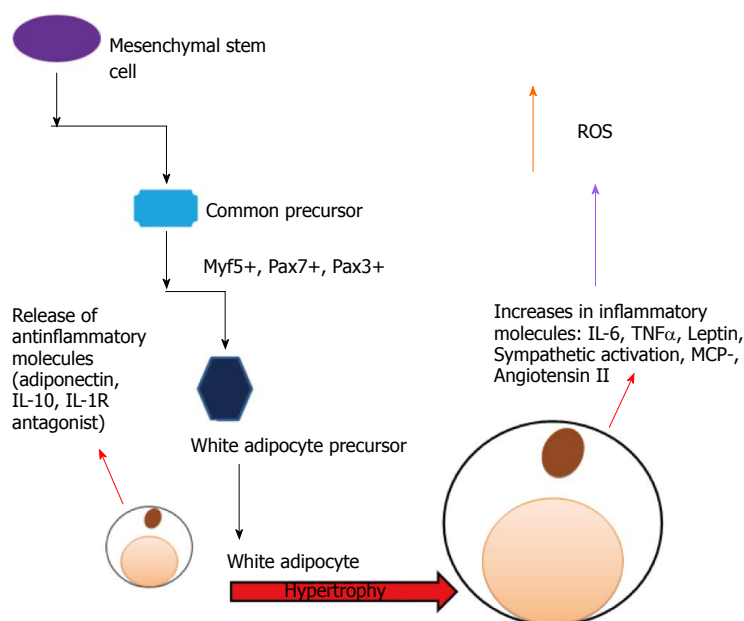


Figure 4 Small adipocytes release anti-inflammatory agents such as adiponectin, interleukin 10, and interleukin 1 receptor antagonist. Hypertrophy of small adipocytes into large adipocytes changes the biochemical release products, into inflammatory markers [interleukin-6 (IL-6), tumor necrosis factor alpha (TNF α), and monocyte chemoattractant protein 1 (MCP1)] and other chemicals such as leptin and angiotensin II that contribute to the disease. Increased activation of the sympathetic nervous system also contributes. IL-10: Interleukin-10; IL-1R: Interleukin 1 receptor; Myf5: Myogenic factor 5; Pax 7: Paired box protein 7; Pax 3: Paired box protein 3; ROS: Reactive oxygen species.

is increased with Ang II level increases^[99,117,118].

Several studies have shown that induction of HO-1 not only decreases weight and obesity, but it can also prevent the development of hypertension, even if its expression is limited to adipocytes^[1,120]. It is not clear if blood pressure is lowered through the indirect effects on the vasculature, kidney, or through the release of other enzymes and factors. If induction of HO-1 is done at any step in the pathway described above, what are the specific effects? If induced during any stage of hypertension, will effects still be seen, or does it need to be induced early in obesity?

Abraham *et al.*^[1], look specifically at the role of HO-1 and the effects it can have on various aspects of obesity. One study specifically examines adipocyte dysfunction; induction of HO-1 can reverse adipocyte dysfunction and to an extent reverse effects of damage^[121]. This lab has also shown significant findings of the role of HO-1 and the attenuating effects it can have with hypertension^[1,122,123]. We have also looked from the other perspective, namely ROS generation. We have recently observed that attenuation of ROS generation with pNaktide^[124,125], a peptide designed to ameliorate the Na/K-ATPase mediated feed forward amplification of ROS^[50], prevents phenotypical changes within adipocytes as well as ameliorates diet induced obesity in mice^[35].

CONCLUSION

There is clearly a very strong relationship between obesity and hypertension. While a plethora of mechanisms potentially link obesity to hypertension, we are left with the provocative possibility that adipocyte biology may play an important role in blood pressure regulation, a topic which to date has not been systematically explored.

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