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Obesity, kidney dysfunction and hypertension: mechanistic links

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Abstract

Excessive adiposity raises blood pressure and accounts for 65–75% of primary hypertension, which is a major driver of cardiovascular and kidney diseases. In obesity, abnormal kidney function and associated increases in tubular sodium reabsorption initiate hypertension, which is often mild before the development of target organ injury. Factors that contribute to increased sodium reabsorption in obesity include kidney compression by visceral, perirenal and renal sinus fat; increased renal sympathetic nerve activity (RSNA); increased levels of anti-natriuretic hormones, such as angiotensin II and aldosterone; and adipokines, particularly leptin. The renal and neurohormonal pathways of obesity and hypertension are intertwined. For example, leptin increases RSNA by stimulating the central nervous system proopiomelanocortin-melanocortin 4 receptor pathway, and kidney compression and RSNA contribute to renin-angiotensin-aldosterone system activation. Glucocorticoids and/or oxidative stress may also contribute to mineralocorticoid receptor activation in obesity. Prolonged obesity and progressive renal injury often lead to the development of treatment-resistant hypertension. Patient management therefore often requires multiple antihypertensive drugs and concurrent treatment of dyslipidaemia, insulin resistance, diabetes and inflammation. If more effective strategies for the prevention and control of obesity are not developed, cardiorenal, metabolic and other obesity-associated diseases could overwhelm health-care systems in the future.

Obesity and its adverse consequences are major burdens to health-care systems worldwide[1]. The Global Burden of Disease study, which includes data from 195 countries, reports that

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the prevalence of obesity has more than doubled since 1980 and parallels global trends in the prevalence of type 2 diabetes mellitus (T2DM)[2,3]. The World Health Organization estimates that in 2016, >1.9 billion adults were overweight, of whom >650 million were obese[4]. In addition, they estimate that >340 million children and adolescents aged 5–19 years and 41 million children under the age of 5 years were overweight or obese in 2016. Historically, obesity was a major health issue only in high-income countries. However, at least one-third of the global population is now overweight or obese and >60% of people with obesity live in developing countries in which the prevalence of hypertension and obesity-associated cardiometabolic disorders is rapidly increasing[4].

People with obesity may now live longer than in previous decades, largely as a result of better health care, and therefore experience a greater number of years with comorbid illnesses such as T2DM, chronic kidney disease (CKD) and hypertension. The lifelong health and economic impact of obesity-associated comorbidities is further amplified by increasing childhood obesity, earlier onset of related chronic diseases and more years spent with comorbid cardiometabolic disorders.

One of the most common comorbid conditions associated with obesity is hypertension, which is a major risk factor for stroke, myocardial infarction, heart failure and CKD[5,6]. Epidemiology studies indicate that 65–75% of primary (essential) hypertension is due to overweight or obesity[7]. In addition, at least 72% of patients with end-stage renal disease (ESRD) have hypertension and/or T2DM, both of which are driven largely by obesity[8]. Although obesity is also an independent risk factor for ESRD, the underlying pathways are not well understood[9,10].

The mechanisms of obesity-induced hypertension have not been fully elucidated, but considerable progress has been made towards unravelling the complex interactions between renal, hormonal and nervous system factors that link excess adiposity with elevated blood pressure (BP). In this Review, we focus on the mechanisms that initiate obesity-induced hypertension rather than on the complex cascade of pathological changes, such as insulin resistance, inflammation, reduced nitric oxide (NO) bioavailability, oxidative stress, lipotoxicity, mitochondrial dysfunction and endoplasmic reticulum stress[10–12], that may cause target organ injury, exacerbate increases in BP and make effective antihypertensive treatment more challenging.

Obesity and cardiometabolic risk

Obesity is most accurately defined as excessive accumulation and/or storage of body fat; however, the most commonly used measure of obesity is body mass index (BMI; weight in kg/height in square metres). People with BMI >30 kg/m^2 are considered obese, whereas those with BMI >25 kg/m^2 are deemed to be overweight. BMI correlates with adiposity and is a convenient metric for use in large population studies; however, BMI has important shortcomings for assessing cardiometabolic risk and does not differentiate muscle from adipose tissue or visceral from subcutaneous fat depots.

Substantial evidence indicates that excess visceral adipose tissue (VAT) conveys a higher risk of cardiometabolic disorders, including hypertension and T2DM, than does excess subcutaneous adipose tissue (SAT), which provides energy-storage depots that protect against fat accumulation in organs[13,14]. In fact, SAT deficiency (for example, lipodystrophy) leads to visceral fat storage and ectopic fat in organs such as the liver, heart and kidneys as well as increased risk of hypertension and cardiometabolic disorders. Surgical removal of excess SAT (for example, large-volume liposuction) does not reduce BP or improve insulin resistance[15]. However, VAT reduction following bariatric surgery (for example, vertical sleeve gastrectomy or Roux-en-Y gastric bypass) rapidly decreases BP[16,17]. Thus, among obese individuals with similar BMI or total body adiposity, those with greater visceral and ectopic fat generally have higher cardiometabolic risk than those with less VAT[13].

Waist circumference is moderately superior to BMI for predicting cardiometabolic risk but can be misleading because this measurement also includes abdominal SAT. Computed tomography (CT) and MRI, although not practical for large population studies, provide more direct estimates of visceral and ectopic fat, which have been called the ‘invisible enemy of cardiometabolic health. Despite their limitations, high BMI and large waist circumference generally predict increased risk of hypertension in population studies. Analysis of body fat location can be used to further refine such risk assessment.

Multiple factors contribute to variations of fat distribution, including genetics, ethnic differences and sex hormones[13,18]. For example, higher levels of testosterone in men than in women may contribute to greater visceral fat storage and increased risk of hypertension and cardiovascular disease (CVD), whereas in women reduced levels of oestrogens may contribute to increased VAT and higher BP postmenopause. Compared with white individuals, Asian individuals may have greater visceral fat and a higher risk of T2DM at lower BMIs[13]. Such observations in different populations have led to recommendations of ethnicity-specific cut-offs for waist circumference and BMI as predictors of cardiometabolic risk[13].

Evidence suggests that excessive adipose deposition around the kidneys (for example, renal sinus fat (RSF) and perirenal fat (PRF)) may be associated with hypertension even after adjustment for traditional risk factors, including overall adiposity and BMI[6,19–21]. Thus, body fat distribution is an important consideration that may explain some of the sex, ethnic and age-related differences in the risk of hypertension that are associated with obesity.

A few studies have suggested that some people who are overweight or obese are metabolically healthy and protected from cardiometabolic disorders[22]. However, other studies with longer-term follow-up (>10–30 years) reported an increased risk of CVD in individuals with overweight or obesity who were previously classified as being metabolically healthy. For example, the Atherosclerosis Risk in Communities study showed that weight gain over a 3-year period was associated with greater rises in BP in metabolically healthy’ individuals with obesity at enrolment than in those with normal weight throughout the study[23]. A 30-year follow-up study of >90,000 women found that most of those who were obese but classified as metabolically healthy at enrolment converted over time to a metabolically unhealthy phenotype that was associated with increased CVD

risk[24]. These and other observations suggest that a progressive conversion of metabolically healthy' to unhealthy phenotypes occurs over several years. Thus, the long-term impact of obesity on hypertension and cardiometabolic diseases is not always apparent in crosssectional studies or in observational studies with short follow-up periods.

Blood pressure responses to obesity

A nearly linear relationship exists between BP and indices of obesity, including BMI, in every population examined, including white, black, Hispanic and Asian populations[6,25]. Studies in primary care settings report that 60–76% of patients who are overweight or obese have hypertension, defined as BP >140/90 mmHg [26]. However, the 2017 American College of Cardiology/ American Heart Association (ACC/AHA) guidelines define stage 1 hypertension as systolic BP 130–139mmHg or diastolic BP 80–89 mmHg [27]. These new criteria will substantially increase hypertension prevalence, especially in younger people with obesity who may have only mild increases in BP before the development of kidney injury.

A study in individuals aged 25–74 years reported that a 1 s.d. increase in BMI over a 5-year period led to a 30% increase in risk of hypertension compared with people whose weight did not change[28]. In the Nurses' Health Study and the Health Professionals Follow-up Study, increases in body weight during 10 years of follow-up were associated with higher risk of hypertension, even within a range of BMIs that were considered normal[29]. In the Johns Hopkins Precursors Study, obesity in young adults conferred a threefold greater risk of hypertension after 46 years of follow-up, even after accounting for changes in lifestyle factors over the life course[30]. Thus, the risk of developing hypertension increases with obesity duration.

Although primary hypertension is closely associated with excess adiposity, some patients who are obese are not considered to be hypertensive. This observation has often been interpreted as evidence that obesity alone is insufficient to cause hypertension and that genetic or epigenetic predisposition and/or other factors are required for obesity to increase BP. However, the search for genetic and epigenetic contributions to obesity-induced hypertension has been disappointing, explaining only a tiny fraction of hypertension[31].

Although genes that mediate obesity hypertension have not been identified, regional body fat distribution is strongly influenced by genetics and in turn may influence susceptibility to cardiometabolic disorders, including hypertension[14]. Some populations seem to be less susceptible to hypertension associated with increases in BMI and overall adiposity than others. For example, Pima Indians have a high prevalence of obesity but relatively low rates of hypertension compared with white individuals32. Muscle sympathetic nervous system activity (MSNA) was also lower in Pima Indians than in white individuals and did not track well with adiposity[33]. However, body weight remained the strongest predictor of BP in Pima Indians[34]. Genetic influences on regional body fat distribution could also contribute to variations in sympathetic activity and BP responses to increasing adiposity in different populations.

Regardless of genetic influences on body fat distribution and BP, the frequency distribution for BP seems to be displaced to higher levels by visceral obesity, increasing the likelihood that BP will be considered hypertensive (FIG. 1). Thus, people who are obese and considered to be normotensive often experience a reduction in BP when they reduce their overall adiposity by losing weight[35]. In addition, most population studies have not measured VAT, RSF and PRF, which are better predictors of increased BP than are BMI or overall adiposity. It would be interesting to determine whether weight reduction lowers BP and sympathetic activity in parallel with reductions in specific fat depots in people who seem to be resistant to obesity-induced hypertension, such as Pima Indians.

Models of obesity-induced hypertension

Several haemodynamic, renal and neurohormonal changes occur during the development of obesity-induced hypertension in humans and in experimental animal models of obesity caused by overfeeding (TABLE 1). These models recapitulate many cardiometabolic abnormalities that are associated with excess adiposity in humans, including insulin resistance, hyperinsulinaemia and dyslipidaemia. Feeding a chronic high-fat diet (HFD) causes reproducible rises in BP in rabbits and dogs, although smaller and less consistent BP increases are observed in rodents[6]. Other cardiovascular, renal, endocrine and sympathetic nervous system (SNS) changes that are associated with obesity caused by an HFD in dogs and rabbits closely mimic those found in people who are obese[6]. However, overfeeding and obesity may rapidly induce cardiorenal changes that are later eclipsed by compensations or pathological changes. For example, renal vasodilation, increases in renal blood flow (RBF) and glomerular hyperfiltration occur early after weight gain but are later followed by declines in RBF and glomerular filtration rate (GFR) as a result of kidney injury and gradual loss of nephrons[10]. Thus, crosssectional studies may not reveal time-dependent cardiorenal changes that initiate the development of obesity-induced hypertension.

Another challenge in this research field is that some animal models may not mimic cardiovascular changes observed in human obesity. For example, many commonly used genetic models of obesity, such as ob/ob and db/db mice and Zucker fatty rats, have derangements of adipokine (for example, leptin) signalling and/or nervous system networks (for example, proopiomelanocortin (POMC)-melanocortin signalling) that mediate sympathetic hyperactivity and hypertension in obesity[6]. In addition, rodents with genetic or diet-induced obesity do not show adherence of fat to the renal capsule and resulting kidney compression as occurs in obese

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Haemodynamic changes in obesity

In addition to elevated BP, obesity is associated with increases in blood and extracellular fluid volumes as well as haemodynamic changes throughout the body. Some of these haemodynamic changes, such as increased muscle tissue blood flow, may be compensations for the higher workloads imposed on the body by excess weight. However, these haemodynamic effects, along with many metabolic changes in obesity, may injure the blood vessels and organs if obesity persists.

Increased cardiac output

Excessive weight gain increases heart rate (HR) and cardiac output (CO) in experimental animals and in humans[35,36] (TABLE 1). In obesity, chronic elevations in resting HR are caused mainly by reduced parasympathetic tone rather than by increases in sympathetic activity or intrinsic HR[6,37].

In rabbits, dogs and humans, obesity increases extracellular fluid volume and blood flow in the gastrointestinal tract, skeletal muscles, heart, kidney and several other tissues, leading to elevated venous return and CO levels[35]. Obesity also causes growth of some tissues and organs such as the heart, kidneys and skeletal muscles owing to increased workload; however, blood flow per gram tissue weight is also increased in some organs such as the kidneys and heart, indicating functional vasodilation that might be partly mediated by increased tissue metabolism and oxygen consumption[6,36].

Despite the increase in blood flow in many tissues under resting conditions, blood flow reserve is reduced in obesity, limiting increases in CO and exercise capacity. Obesity and prediabetes also cause endothelial dysfunction, which is reversible with weight loss if severe vascular injury has not occurred[38,39]. Accelerated vascular stiffening also occurs in obesity, leading to increases in pulse wave velocity and systolic BP[40]. The adverse impact of obesity on blood vessels is associated with increased BP and metabolic disorders such as hyperglycaemia and hyperlipidaemia, oxidative stress, inflammation and stimulation of various neurohumoral systems[39].

Cardiac hypertrophy

Haemodynamic changes in obesity, including hypertension, increased venous return and increased CO levels, predispose the heart to left ventricular hypertrophy (LVH) with

increased wall thickness and chamber size. Thus, obesity is associated with eccentric and concentric LVH[36,41]. Enlargement of the atria also occurs in obesity and is related, in part, to volume expansion, increased venous return and cardiac preload[36]. These cardiac changes markedly increase the risk of heart failure and arrhythmias.

Renal haemodynamics

Increased RBF also contributes to increases in venous return and CO in individuals with obesity[6]. Excessive weight gain initially causes renal vasodilation and increases in RBF and GFR before nephron injury[35]. Obesity-induced glomerular hyperfiltration is associated with vasodilation of renal afferent arterioles and increased glomerular hydrostatic pressure, similar to that observed in diabetes mellitus and hyperglycaemia[35,42].

Multiple factors could contribute to renal vasodilation in obesity, including compression of the renal tubules, hyperglycaemia, high protein intake, hyperinsulinaemia and increased BP combined with impaired renal autoregulation[6,43,44]. Altered macula densa feedback (also called tubuloglomerular feedback) may link several of these factors to afferent arteriolar vasodilation. An increase in NaCl reabsorption in the renal tubules before or at the macula densa cells results in a decrease in NaCl concentration at these cells, which, in turn, send signals to the renal afferent arterioles that cause vasodilation as well as increases in GFR and RBF. As discussed further below, obesity may lead to compression of the kidneys, resulting in increased intrarenal pressures and tending to reduce blood flow rates in the vasa recta and loop of Henle[35,45] (FIG. 2). These changes tend to increase fractional NaCl reabsorption in the loop of Henle and decrease delivery of NaCl to the macula densa, causing feedback-mediated reductions in afferent arteriolar resistance, increases in RBF and GFR and stimulation of renin secretion from juxtaglomerular cells[10]. Compensatory increases in GFR and elevated BP help to restore macula densa NaCl delivery towards normal, permitting sodium balance to be re-established despite increased NaCl reabsorption in the loop of Henle. Hyperglycaemia and high protein intake, which are often associated with obesity, may also cause afferent arteriolar vasodilation and increased GFR via macula densa feedback[44,46].

Mineralocorticoid receptor (MR) activation may also contribute to renal vasodilation in obesity. We showed that MR blockade markedly attenuated glomerular hyperfiltration in obese dogs fed an HFD[47]. Moreover, aldosterone activates MRs expressed on macula densa cells and increases their production of NO, which induces renal vasodilation and glomerular hyperfiltration[48,49]. Consistent with these findings, blockade of NO synthesis abrogated glomerular hyperfiltration in dogs with aldosterone-induced hypertension[50].

The increased BP that is associated with obesity may also contribute to increases in glomerular hydrostatic pressure and GFR, especially if renal autoregulation is impaired because of attenuated macula densa feedback. Despite the adaptive value of glomerular hyperfiltration in offsetting renal sodium reabsorption in obesity, elevated glomerular hydrostatic pressure may eventually contribute to renal injury.

Increased renal sodium reabsorption

Excessive sodium reabsorption by the kidneys initiates the sodium retention, increased extracellular fluid volume and elevated BP that are associated with excess weight gain. Although a balance between the intake and renal output of sodium is eventually achieved, individuals who gain excess adiposity maintain sodium balance at higher BPs than when they were lean, indicating impaired renal-pressure natriuresis[16,51]. In the early phases of obesity, BP may not be salt-sensitive; therefore, hypertension may not be greatly exacerbated by high salt intake[10]. By contrast, in chronic obesity, increases in BP, glomerular hyperfiltration, neurohumoral activation and metabolic changes may cause renal injury and increased salt sensitivity of BP.

At least three mechanisms have important roles in causing the increased renal sodium reabsorption and hypertension that are associated with rapid increases in adiposity and excessive weight gain: renal compression; stimulation of the renin-angiotensin-aldosterone system (RAAS) and renal MR activation; and stimulation of the SNS (FIG. 3). These mechanisms and other factors that contribute to the development of obesity-induced hypertension are discussed in more detail below.

Renal compression

Excessive VAT initiates several effects that may compress the kidneys, increase renal sodium reabsorption and raise BP. Pressure in the abdominal cavity may be elevated to >40 cm H_20 in patients with large sagittal abdominal diameters[52]. In addition, excess PRF encapsulating the kidneys and excess RSF may squeeze the kidneys and increase intrarenal pressures[10,35].

In the Dallas Heart Study, increased VAT, but not total or subcutaneous adiposity, was strongly associated with incident hypertension during a median follow-up of 7 years[21]. However, increases in PRF and RSF increased the risk of hypertension independent of BMI and VAT. After accounting for other body fat depots and risk factors for hypertension, RSF volume was highly correlated with the number of BP medications and with stage II hypertension[19]. In 2,923 participants from the Framingham Heart Study, high RSF levels (fatty kidney) conveyed a 2.2-fold increased risk of hypertension[20]. High levels of RSF were also associated with a 2.3-fold increased risk of CKD after adjusting for VAT and BMI[20].

As the kidneys are surrounded by a tight capsule, expansion of the extracellular matrix (ECM) in the kidney medullae could also contribute to renal compression and increased intrarenal tissue pressure[53]. In obese rabbits, dogs and humans, the levels of renal medullary glycosaminoglycans, especially hyaluronan, which is an important component of the ECM and is often associated with tissue inflammation and oedema, were markedly elevated compared with lean controls[53–55]. Increases in total tissue pressure and interstitial fluid hydrostatic pressure to −19 mmHg have been observed in obese dogs[56]. As discussed above, such pressure increases could compress the vasa recta and thin loops of Henle, resulting in reduced blood flow in the kidney medulla and contributing to increases in fractional NaCl reabsorption, renin secretion and glomerular hyperfiltration (FIG. 2).

Excessive RSF and PRF may also cause lipotoxicity owing to the accumulation of intracellular triglycerides and toxic metabolites such as ceramides[57,58]. The mechanisms by which ectopic fat in the kidneys causes injury are still unclear, but increased levels of reactive oxygen species (ROS), mitochondrial dysfunction and endoplasmic reticulum stress may be important contributors.

Excess PRF and RSF cannot explain the increases in BP that occur shortly after rapid increases in caloric intake; however, kidney compression and the lipotoxicity of RSF and PRF may help to explain why VAT is more strongly associated with hypertension than is SAT. Kidney compression likely contributes to hypertension in obese rabbits, dogs and humans, but this mechanism is not important in obese rodents, which have little fat adherence to the kidney capsule or renal compression[6]. Why rodents are protected from fat invasion into the renal sinuses and fat adherence to the kidney capsule is unknown.

Activation of the RAAS and MR

Experimental animals and people with obesity generally have modest increases in most components of the RAAS, including angiotensin II (AngII) and aldosterone[6,59]. Stimulation of the RAAS in obesity occurs despite sodium retention and increased BP, which normally inhibit renin secretion, AngII formation and aldosterone secretion.

Angiotensin II

Current evidence suggests that mild elevations in AngII levels in obesity are driven largely by increased renal renin secretion due to SNS activation, kidney compression and perhaps other factors such as adipokines[51,60]. Adipose tissue has been suggested to produce substantial amounts of AngII in obesity[61]. Although adipocytes may produce angiotensinogen, which is cleaved by renin to produce angiotensin 1 (a precursor for angiotensin 11), it is not clear whether adipose tissue produces enough AngII to influence BP regulation or make a major contribution to obesity-induced hypertension.

Although obesity causes only modest increases in AngII formation, pharmacological RAAS blockade blunts sodium retention and hypertension in obesity[6]. For reasons that are still unclear, obesity enhances BP sensitivity to AngII[62]. Renal sodium reabsorption is stimulated by low levels of AngII that act via direct effects on several NaCl transporters and by inducing constriction of efferent arterioles. In addition to increasing reabsorption of sodium in peritubular capillaries, efferent arteriolar constriction increases glomerular hydrostatic pressure, exacerbating the adverse effects of increased BP and afferent arteriolar vasodilation on glomerular stress[63].

As mentioned above, blockade of the RAAS with AngII receptor blockers, angiotensin-converting enzyme (ACE) inhibitors or renin inhibitors reduces BP in patients with obesity and hypertension[64–66]. Although most major hypertension clinical trials have included RAAS blockers as part of the treatment regimens, to date, no large randomized clinical trials have compared the efficacy of RAAS blockers with other antihypertensive agents in lean and obese patients.

Antagonism of the RAAS with ACE inhibitors or AngII receptor blockers also attenuates, but may not completely halt, the progression of kidney injury in patients with obesity, hypertension and T2DM[67,68]. The renoprotective effect of RAAS blockers in this setting is partly related to BP reduction but might also be due to efferent arteriolar dilation, which lowers glomerular pressure.

Aldosterone and MR activation

Elevated concentrations of plasma aldosterone in obesity might partly be a result of AngII stimulation of adrenal aldosterone secretion. However, adipocyte-derived factors such as leptin may also stimulate the adrenal gland to produce aldosterone[69]. Studies in rodents have provided evidence of sex differences in the role of adipocyte-derived factors in aldosterone secretion. In obese female rats, leptin may contribute to increased BP and endothelial dysfunction by stimulating secretion of aldosterone[70,71]. However, the importance of leptin-induced increases in aldosterone secretion in the setting of obesity in male rodents or in humans of either sex is still unclear.

Although obesity is often associated with only mild increases in plasma aldosterone levels, MR blockade effectively reduces BP and attenuates injury in target organs including the kidneys. In dogs fed an HFD to produce obesity, MR antagonism with eplerenone blunted sodium retention, glomerular hyperfiltration and the development of hypertension by >50%[47]. In patients with obesity and hypertension, MR antagonism with spironolactone reduced BP and urinary albumin excretion even after long-term blockade of AngII formation with ACE inhibitors[72]. Moreover, in patients with obesity and treatment-resistant hypertension who were treated with spironolactone, the resulting reductions in BP did not correlate with plasma aldosterone concentration[73,74]. In addition, MR antagonism improved brachial artery flow-mediated dilation (an index of vascular endothelial function)[75] and left ventricular function in patients with obesity and left ventricular diastolic dysfunction[76]. These studies indicate that MR antagonism is an important therapy for obesity-induced hypertension and its associated cardiorenal abnormalities even in the absence of hyperaldosteronism.

Aldosterone synthase inhibitors have been shown to attenuate cardiac and renal injury in models of experimental hypertension, such as spontaneously hypertensive rats (SHRs) and uninephrectomized rats fed a high-salt diet[77,78], but their efficacy in obesity-induced hypertension is unclear. A randomized controlled trial in patients with primary hypertension showed that treatment with the aldosterone synthase inhibitor LCI699 reduced serum aldosterone levels and BP[79]. The BP-lowering effect of LC1699 was not as impressive, however, as that observed with MR antagonism, and LC1699 therapy was associated with an important adverse effect of reduced cortisol synthesis. Another study in patients with resistant hypertension and an average BMI of −32 kg/m^2 reported that aldosterone synthase inhibition using LC1699 reduced plasma aldosterone concentration but caused minimal reductions in BP that were substantially less than those achieved with an MR antagonist[80]. Preclinical studies in mice suggest that aldosterone synthase inhibition may amplify diet-induced hyperinsulinaemia and obesity[81]; such adverse effects have not been reported for MR antagonists.

The finding that MR blockade lowers BP and protects against target organ injury in obesity even when plasma aldosterone concentration is not elevated or is reduced due to AngII blockade, together with observations that MR antagonists may be more effective than aldosterone synthesis inhibitors for lowering BP in resistant hypertension, raises the question of whether MR activation in obesity is due to factors other than aldosterone (FIG. 4). Several potential factors have been suggested, including small GTP-binding protein Racl, a member of the Rho family of GTPases[82]. Racl stimulates MR signalling, and the levels of Racl in renal epithelial cells were increased in obese rodents. In addition, Racl inhibitors ameliorated proteinuria and kidney injury in obese rodents and in rodents with salt-sensitive hypertension[82]. Although the factors that regulate Racl expression are not entirely clear, adipocyte-derived cytokines, hyperglycaemia and oxidative stress are thought to induce Raci expression in obesity[82].

MR can also be activated by glucocorticoids in the setting of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) deficiency[83]. 11βHSD2 colocalizes with MR in the collecting tubules and converts cortisol, which has a high affinity for the MR, to cortisone, which is relatively inert at the MR. In obese dogs, kidney 11βHSD2 expression is reduced by 60–70%, supporting the possibility that glucocorticoids might contribute to MR activation in obesity[6]. Other studies suggest that increased oxidative stress and changes in the renal epithelial intracellular redox state may permit cortisol to activate the MR[84]. Whether glucocorticoids and Racl have a major role in mediating MR activation in obesity-induced hypertension is uncertain.

Regardless of the precise mechanisms by which MR antagonism reduces BP in obesity-induced hypertension, this treatment clearly offers benefit for patients in which BP cannot be adequately controlled using other antihypertensive therapies. The landmark PATHWAY-2 trial[85,86] clearly established that the MR antagonist spironolactone is effective for treating patients with resistant hypertension who are usually overweight or obese and already on at least three antihypertensive drugs[87]. The antihypertensive benefit of MR antagonism seems to be related largely to its natriuretic and diuretic effects[86], which are consistent with the important role of MR activation in mediating obesity-associated sodium retention[88].

Natriuretic peptide deficiency

Natriuretic peptides (NPs), including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are secreted from the heart in response to stretch of the atrial or ventricular cardiomyocytes and signal via cGMP-coupled receptors[89]. As NPs are known to reduce sodium reabsorption and BP, relative NP deficiency has been postulated as a contributor to the pathogenesis of obesity-induced hypertension. Men with obesity and hypertension had lower plasma pro ANP levels than normotensive lean men despite greater sodium intake and larger left atria[90,91]. Increases in NPs associated with high salt intake and volume loading are also diminished in obese compared with lean individuals[90–92]. In the Framingham Heart Study, participants with obesity had lower circulating amino-terminal pro-ANP concentrations than those who had normal BMI[93]. Other studies, however, found no correlation or even a positive correlation between BMI and plasma NP concentrations[94,95].

As cardiac filling pressures, atrial volumes and ventricular volumes are generally elevated in obesity, increased NP secretion in individuals with obesity would be expected. However, other factors such as increased degradation and/or clearance of NPs by adipocyte-derived neprilysin (an endopeptidase) may tend to reduce plasma NP levels and cause a relative deficiency in obesity. Obesity may also upregulate NP receptor-C (NPR-C), which is highly expressed in adipose tissue and functions as a scavenger receptor to facilitate cellular NP uptake and degradation without contributing to increased guanylyl cyclase activity[89]. Thus, increased levels of neprilysin and upregulation of NPR-C in obesity could contribute to a relative NP deficiency and impaired NaCl homeostasis despite increased cardiac filling pressures and volume loading.

Cardiac-derived NPs have also been postulated to regulate metabolism[96,97]. They have been reported to promote lipid mobilization from adipose tissue as well as postprandial lipid oxidation[96,97], suggesting that relative deficiency of NPs could contribute to accumulation of adipose tissue and associated metabolic disorders[89]. Consistent with this hypothesis, transgenic mice that overexpressed BNP were protected against diet-induced obesity and insulin resistance[98]. In addition, genetically engineered mice with increased circulating levels of ANP and BNP (owing to a lack of receptors that promote clearance of these NPs) showed ‘beiging of white adipocytes and increased thermogenesis compared with wild-type mice[99]. These observations suggest that NPs may protect against obesity and metabolic dysfunction, whereas NP deficiency could exacerbate obesity-induced metabolic disorders. However, additional research is needed to clarify the physiological importance of abnormal secretion and clearance of NPs in obesity-induced hypertension.

Gut hormones and the microbiota

The gut mucosa is a dynamic reservoir of microbiota that are constantly modified by diet, drugs, toxins, pathogens and other factors. Alterations in the gut microbiota (GM) have been suggested to have pathophysiological roles in obesity by altering host energy harvest and storage[100]. Individuals with obesity may have decreased bacterial diversity, and gut microbial dysbiosis is associated with metabolic disorders such as T2DM[101]. Although an altered GM clearly occurs secondary to changes in diet and subsequent development of obesity, a causal relationship between an altered GM and obesity has also been suggested on the basis of the findings of GM transplantation experiments[102].

Gut dysbiosis has also been reported in experimental animals and patients with hypertension, and complex interplay among the GM, immune system, blood vessels, kidney and brain has been postulated to contribute to the pathogenesis of this disease[103]. In mice, high salt intake altered the GM, and treatment with *Lactobacillus murinus* attenuated salt-induced increases in BP by ~5 mmHg [104]. The mechanism for the effect of altered GM on BP was postulated to involve induction of T helper 17 (T_H17) cells and an autoimmune response[104]. A pilot study in normotensive, healthy humans reported that a high-salt diet for 14 days reduced intestinal survival of *Lactobacillus* and increased BP, although a cause-and-effect relationship between altered GM and BP was not established[104]. In SHRs, BP reduction as a result of ACE inhibition had beneficial effects on gut pathology (for example, reductions in mucosal permeability, inflammation and dysbiosis)[105]. These findings suggest

that an altered GM may be, in part, secondary to increased BP or activation of the RAAS and SNS, which are known to contribute to hypertension in SHRs.

The GM produces unique metabolites that may influence BP regulation. In particular, digestion of dietary fibre by the GM produces short-chain fatty acids (SCFAs) including acetate, propionate and butyrate. These SCFAs are thought to affect the function of the immune system, epithelial cells, blood vessels and nervous system and may underlie the reductions in hypertension risk that are associated with fibre-rich diets[103,106]. Although production of SCFAs provides a plausible link between the GM and BP regulation, limited direct evidence exists for a cause-and-effect relationship in obesity-induced hypertension.

Another potential mechanism by which the GM might influence BP regulation is via the enteric nervous system (ENS), which controls gut motility in coordination with the autonomic nervous system[103]. The ENS communicates bi-directionally with the central nervous system (CNS), receiving sympathetic and parasympathetic input and sending neurohormonal signals. The vagus nerve sends sensory signals to the brainstem nucleus tractus solitarius (NTS), which is a major CNS centre for cardiometabolic regulation. However, the importance of GM-induced vagal afferent signals in BP control is uncertain.

The GM and/or its associated metabolites may also alter the release of gut hormones that have been implicated in a wide range of actions that could influence BP regulation[107,108]. For example, glucagon-like peptide-1 (GLP1), which is generated from L-cells in the colon and ileum, increases insulin secretion and insulin sensitivity, reduces food intake and increases renal NaCl excretion[109]. The GLP1 agonist liraglutide and dipeptidyl peptidase 4 (DPP4) inhibitors, which attenuate degradation of GLP1, lower BP in obese animals and in patients with hypertension and T2DM[108]. Gastrin, a hormone that is released from stomach G-cells, has also been postulated to influence BP regulation by promoting natriuresis[108].

Although the potential for the GM, its associated metabolites and gut hormones to participate in cardiometabolic regulation has generated considerable interest, limited direct evidence exists for a major role of these factors in obesity-induced hypertension or for major beneficial effects of GM manipulation (for example, through faecal transplants or the use of antibiotics or probiotics) for treatment of patients with hypertension. However, this research field is rapidly evolving. The complexity of the GM and its metabolites as well as its far-reaching effects on the neurohormonal and immune systems suggest a plausible role of these factors in cardiovascular regulation.

Adipokines

Adipocytes are much more than just energy-storage depots — they secrete many bioactive substances that influence metabolic and cardiovascular functions, including BP[110]. Adipose tissue remodels and expands in obesity to accommodate excessive energy intake while markedly altering its secretion of adipokines. The pathogenic role of VAT, beyond its contributions to overall adiposity, may be related to secretion of cytokines such as tumour necrosis factor (TNF) and IL-6 [14] that contribute to inflammation, insulin resistance and

increased BP. In addition, macrophages infiltrate VAT to a greater extent than SAT and secrete TNF and other pro-inflammatory molecules that could influence BP[14].

Evidence suggests that reduced adipose tissue quality (increased lipid density and adipocyte size) may convey cardiometabolic risk. Increased VAT and SAT volume as well as reduced adipose tissue quality (assessed indirectly as reduced attenuation in Hounsfield units on CT) were reported to be associated with increased cardiovascular risk that was not explained by increased BMI[111]. Reduced fat attenuation on CT may represent more lipid-dense tissue and increased adipocyte size owing to an inability to proliferate new adipocytes. Larger adipocytes are generally thought to secrete more inflammatory adipokines and to be associated with greater cardiometabolic risk than smaller ‘healthy adipocytes.

Reduced fat attenuation may also reflect decreased vascularity as blood has a higher attenuation with CT than does fat[111]. Decreased vascularity could cause hypoxia, increased inflammation and the release of additional pathogenic cytokines. Reduced adipose tissue quality (larger adipocytes) might also suggest a limited capacity for adipocyte hyperplasia, leading to ectopic fat deposition in organs such as the kidneys, liver and heart and causing lipotoxicity through altered release of adipokines or toxic substances from lipid metabolism, such as ceramides[112].

Adiponectin

Adiponectin is an adipocyte-secreted protein hormone that promotes glucose metabolism and fatty acid oxidation[113]. Plasma adiponectin concentration is decreased in patients with obesity, especially those with excess visceral fat, and this downregulation is associated with insulin resistance, impaired glucose metabolism, decreased fatty acid metabolism and ectopic fat accumulation[114,115]. Reduced plasma adiponectin concentrations have also been postulated to cause endothelial dysfunction and activation of the RAAS and SNS in obesity[12,114,115]. In humans, the association between hypoadiponectinaemia and hypertension has been widely studied but remains controversial. Ethnicity may be an important factor in determining the importance of hypoadiponectinaemia as decreased adiponectin levels are associated with hypertension in Asian individuals but not in white individuals[116].

The role of adiponectin in cardiometabolic regulation was examined in adiponectin-knockout mice, which had normal BP when maintained on a normal salt intake[117]. By contrast, when fed a high-salt diet, these mice had greater increases in BP than did control mice, suggesting salt sensitivity of BP. Adiponectin supplementation reduced BP in salt-fed, adiponectin-knockout mice and in KKAy mice, which develop obesity via ectopic expression of agouti protein[117]. Whether adiponectin deficiency causes hypertension in humans or experimental animals with obesity has not yet been determined. Thus, whether hypoadiponectinaemia is just a biomarker of obesity-induced hypertension or whether reduced levels of adiponectin lead to increases in BP is unclear[118].

Leptin

Leptin is a hormone that is produced mainly by adipocytes and has been implicated in a wide variety of physiological functions, especially in the regulation of energy balance[119,120].

In contrast to adiponectin, leptin is secreted in increasing amounts as adipocytes enlarge[119,120]. In addition to regulating energy stores, leptin increases sympathetic nerve activity (SNA) by binding to leptin receptors (LepRs) in the CNS and contributes to obesity-induced hypertension[6,121,122]. Plasma leptin concentration is highly correlated with SNA activity[123], and acute leptin infusions increase SNA in the brown adipose tissue, adrenal glands and kidneys of rodents[124]. Leptin infusions in rodents over several days also cause mild, gradual increases in BP and HR[125–127]. The slowly developing BP effects of chronic leptin infusions are consistent with mild SNS activation that does not cause vascular constriction but may increase renal NaCl reabsorption. Combined blockade of both a-adrenergic and β-adrenergic receptors abolished the chronic effects of leptin on BP in male rats, suggesting that these effects were mediated by the SNS[128]. However, as mentioned above, leptin-induced increases in aldosterone secretion may also contribute to the chronic BP effects of leptin infusion in female rodents[71].

The chronic hypertensive effects of leptin in non-obese rodents are modest; however, hyperleptinaemia also causes anorexia and stimulates NO production, effects that tend to decrease SNA and BP[127]. The chronic hypertensive effects of leptin were greatly potentiated after inhibition of NO synthesis despite weight loss that was associated with decreased food intake[127]. As obesity may cause endothelial injury, impaired NO bioavailability and resistance to the anorexic effects of leptin, the BP actions of leptin could be enhanced in obesity assuming that stimulation of SNA is preserved as has been previously reported[126].

The observation that LepR antagonism decreased BP and SNA in obese rabbits supports the importance of leptin in obesity hypertension[129]. In addition, leptin-deficient (ob/ob) mice exhibit severe obesity, dyslipidaemia, insulin resistance and hyperinsulinaemia but reduced BP and SNA compared with lean control mice[130]. Leptin infusion in ob/ob mice raised their BP despite causing significant weight loss[131]. Together, these observations suggest that leptin increases sympathetic activity and BP in obese rodents.

The importance of leptin in mediating human obesity-induced hypertension is not yet clear. Similar to findings in rodents, acute leptin administration stimulates SNA in humans[132]. Although the effect of chronic leptin infusion on SNA in humans has not yet been reported, administration of recombinant leptin for 12 weeks failed to increase BP in overweight or obese adults[133]. However, BP was not a primary outcome in these studies, and the dose of leptin that was used also failed to alter body weight. A study that included four patients with leptin deficiency due to gene mutations found that despite severe obesity, three of these patients had normal BP and only one had high BP, possibly owing to unexplained high levels of adrenocorticotropic hormone, which can increase plasma cortisol levels as well as BP[134]. Moreover, these leptin-deficient individuals displayed evidence of autonomic dysfunction, including postural hypotension, reduced BP responses to cold pressor stimuli and diminished RAAS responses to upright posture. Thus, current data, although sparse, suggest that leptin increases SNA in humans and that people with leptin deficiency may not be hypertensive or have increased SNA despite severe obesity, insulin resistance, hyperinsulinaemia and dyslipidaemia. These observations, together with the findings in rodents discussed above, are consistent with the concept that leptin may act as a link between obesity, SNA and hypertension.

Differential effects of leptin on blood pressure and metabolic functions.—The anorexic effects of acute leptin injections are attenuated in individuals with obesity[135]. Multiple factors may contribute to such leptin resistance, including saturation of leptin transport through the blood-brain barrier and attenuated post-receptor signalling, which have been postulated to attenuate the effects of leptin on the CNS.

Although the suppressive effects of leptin on food intake are blunted in obesity, its acute stimulatory actions on RSNA seem to be preserved, suggesting selective leptin resistance[126,136]. The sensitivity of BP and SNA to chronic hyperleptinaemia is not as clear. We found that in rodents, HFD-induced obesity blunts the acute anorexic effects of leptin but does not cause resistance to the chronic CNS effects of leptin on BP or HR[137]. To date, comparable studies in humans have not been reported and the neuronal and intracellular signalling pathways that may mediate selective leptin resistance in obesity are unclear.

Activation of the LepR in different neuronal populations likely contributes to variable control of cardiometabolic functions in obesity. The LepR is expressed in multiple regions of the forebrain and hindbrain, including the hypothalamus, brainstem vasomotor centres and intermediolateral nucleus (IML) of the spinal cord[119,135,138] (FIG. 5a). Although precise mapping of CNS centres responsible for the effects of leptin on autonomic and cardiometabolic function is still lacking, extra-hypothalamic as well as hypothalamic centres have been implicated[120,126]. Deletion of LepR in the hypothalamic arcuate nucleus (ARC) of mice blocked much of the elevated RSNA that was evoked by leptin[139]. Selective LepR deletion in POMC neurons of the ARC and brainstem also abolished BP increases in mice during chronic leptin infusions[140]. Acute leptin injections into the brainstem NTS doubled RSNA and significantly increased BP, suggesting that brainstem LepRs also contribute to the effect of leptin on SNA[138]. Thus, the SNS effects of leptin may involve multiple neuronal populations.

In the CNS, leptin increases Janus tyrosine kinase 2 (JAK2) activity and activates three primary intracellular pathways: phosphorylation of LepR at Tyrl 138 recruits latent signal transducer and activator of transcription 3 (STAT3); phosphorylation of LepR at Tyr985 recruits Src homology 2 tyrosine phosphatase (SHP2) to activate mitogen-activated protein kinase (MAPK); and autophosphorylation of JAK2 activates insulin receptor substrate 2 (IRS2)-phosphatidylinositol 3-kinase (PI3K) signalling[119] (FIG. 5b). Although genetic deletion of these CNS signalling pathways may increase adiposity, only STAT3 deletion causes severe obesity and greatly attenuates the anorexic effect of leptin[141]. Targeted STAT3 deletion in POMC neurons markedly blunted the BP effect of leptin in mice but caused only small reductions in energy expenditure and increases in food intake[142]. Thus, leptin-mediated STAT3 activation in POMC neurons contributes to regulation of BP, whereas STAT3 signalling in other neurons seems to mediate most of the effects of leptin on energy expenditure and food intake.

The IRS2-PI3K pathway also contributes to the effects of leptin on SNA and BP. The acute stimulatory effect of leptin on RSNA in anaesthetized mice was nearly abolished by pharmacological inhibition of PI3K[143]. Genetic deficiency of CNS IRS2 signalling greatly diminished the BP effects of chronic leptin infusion but elicited only mild increases in

adiposity and failed to attenuate the anorexic effects of leptin in mice[144]. Thus, IRS2-PI3K signalling has an important role in mediating the effects of leptin on SNA and BP, but it has much less effect on energy balance.

Neuronal deletion of SHP2 signalling in mice led to hyperphagia, severe obesity and glucose dysregulation[145]. Moreover, targeted deletion of SHP2 in the forebrain or in POMC neurons markedly attenuated increases in BP and lowering of glucose levels in response to chronic leptin infusion, indicating an important role for SHP2 signalling in these cardiometabolic functions[146,147].

Thus, each of leptin's three main cell signalling pathways mediate BP regulation; however, they have different actions on control of energy balance and glucose levels. A potential explanation for selective leptin resistance is that these three pathways are regulated differentially in obesity; however, this hypothesis has not yet been rigorously tested. POMC neurons are critical for the effects of leptin on glucose regulation, RSNA and BP, whereas other hypothalamic, and perhaps brainstem, neurons seem to have a major role in mediating the effects of leptin on energy balance and body weight regulation. How these different neuron populations interact, how their signalling pathways are regulated, whether selective leptin resistance occurs in obesity and the mechanism of selective leptin resistance remain unclear.

Regulators of leptin signalling.—An important regulator of LepR signalling is protein tyrosine phosphatase IB (PTP1B), which dephosphorylates JAK2 (FIG. 5b). Genetic disruption of PTP1B signalling enhances leptin signalling and attenuates diet-induced obesity but amplifies the effects of leptin on BP[148]. Surprisingly, POMC-specific PTP1B deficiency did not enhance BP and HR responses to hyperleptinaemia induced by an HFD but did improve glucose tolerance in male mice[149]. The observation that PTP1B deficiency increases BP via SNS stimulation, even when leptin concentrations are not elevated[148], indicates that this pathway influences SNA and BP through mechanisms other than leptin signalling.

Suppressor of cytokine signalling 3 (SOCS3) deficiency also enhanced leptin signalling and reduced adiposity in mice maintained on an HFD[150]. In addition, neuronal SOCS3 deficiency reduced body weight and food intake, amplified the effects of leptin on BP and attenuated the adverse metabolic effects of a high-fat, high-fructose diet in mice[151]. These observations suggest that PTP1B and SOCS3 may modulate the cardiometabolic effects of leptin, but their combined contribution to obesity-induced selective leptin resistance is still unknown.

In summary, obesity elicits complex alterations in renal, SNS, endothelial and vascular function that may augment the effects of leptin on SNA and BP. However, obesity also attenuates the effects of leptin on appetite, energy expenditure and glucose homeostasis. The extent to which selective leptin resistance occurs in obesity is unclear, but the net effect may be preservation or even amplification of leptin's hypertensive effects and attenuation of its beneficial anorexic and antidiabetic actions that help to control body weight and prevent metabolic dysfunction.

Increased sympathetic nerve activity

The role of the SNS in linking obesity with elevated BP has been well documented in experimental models and in humans[121,152]. Although obesity is generally associated with increased SNA, sympathetic stimulation is not uniform in different organs. In humans, skeletal MSNA, measured by microneurography, increases even with modest weight gain[153]. RSNA, assessed by kidney noradrenaline spillover, is also higher in individuals with obesity than in those who are non-obese and normotensive[152,154]. In rabbits, RSNA increases within a few days of starting an HFD[155]. In contrast to skeletal muscle and kidneys, heart SNA may be within the normal range, or perhaps even reduced, in patients with obesity and hypertension[152]

Considerable variability exists in SNA and BP among individuals with obesity of similar age, sex and BMI. Part of this variability may relate to differences in VAT, which seems to be more closely correlated with increased SNA and hypertension than does overall adiposity[156]. Sex and age-related variations in body fat distribution may also contribute to differences in SNA between women and men, and between younger and older adults[157]. Major challenges for quantitatively assessing SNA and its relationship to obesity-induced hypertension include difficulties in accurately measuring SNA in various organs; difficulties in measuring SNA during normal daily activities rather than just under resting conditions; and differences in body fat distribution and fat depots that influence SNA but are often not assessed.

Increases in SNA that are associated with obesity are often modest, vary between organs and do not reduce tissue blood flow. However, sympathetic blockade in patients with obesity or in experimental animals with dietary-induced obesity consistently reduces BP[6,158]. These findings indicate that increased sympathetic activity is an important contributor to the development and maintenance of obesity-induced hypertension.

The role of renal nerves

The renal nerves may mediate most of the BP effects of sympathetic activation in obesity. Increased RSNA in individuals with obesity contributes to increases in renin secretion, sodium reabsorption and BP[159–161]. Much of the evidence for a role of increased RSNA in obesity-induced hypertension comes from the findings of renal denervation (RDN) studies. In obese dogs fed an HFD, RDN greatly attenuated sodium retention and increases in BP[159]. RDN also nearly normalized BP in dogs with established obesity-induced hypertension[160,162] (FIG. 6). Moreover, partial RDN, using a catheter-based radiofrequency method, reduced renal noradrenaline levels by only ~42% but substantially decreased BP in obese dogs[161]. Studies in rodent models of obesity-induced hypertension also demonstrated reductions in BP and protection against target organ injury after RDN[163].

In overweight or obese patients with resistant hypertension, catheter-based radiofrequency RDN lowered office systolic/diastolic BP by −25 to −30/−10 to −12 mmHg for up to 24 months[164]. In the SYMPLICITY HTN clinical trials, RDN also decreased 24-hour ambulatory systolic/diastolic BP by −11/−7mmHg [164]. The first randomized, sham-controlled RDN trial, SYMPLICITY HTN-3, failed to prove superiority of RDN for BP

lowering compared with a sham control procedure[165]. However, all of these clinical trials were confounded because the extent of RDN was not verified and patients were already on at least three BP medications, including antagonists of the RAAS, which contributes to the BP effect of RSNA. In overweight patients with hypertension who were not taking antihypertensive medications, endovascular ultrasound RDN caused significantly greater reductions in 24-hour ambulatory systolic BP at 2 months than did a sham procedure[166]. However, this trial was also limited because the extent of RDN was not assessed.

Even under optimal conditions, catheter-based RDN methods ablate only 40–50% of renal nerves unless nerves running along the renal segmental arteries are also ablated[167]. A study of patients receiving medical treatment for moderate, uncontrolled hypertension indicated that RDN extending into branch arteries caused significant, clinically relevant reductions in BP compared with sham controls[168]. Thus, in patients and in experimental animals with obesity hypertension, RDN lowers BP if the nerves are ablated along the branches as well as the main renal artery. However, the BP-lowering effects of RDN may be attenuated by prior antihypertensive therapy, especially RAAS blockade.

RDN removes both sympathetic efferent and sensory afferent renal nerves. Increased stimulation of renal sympathetic efferent nerves is recognized to increase renin secretion, renal tubular sodium reabsorption and BP. However, sensory afferent fibres convey signals from renal chemoreceptors and mechanoreceptors to the CNS and are thought to contribute to increased BP in some forms of experimental hypertension[169]. The hypothesis that renal afferents mediate some of the BP effects of RDN in humans was sparked by the finding that whole-body noradrenaline spillover and MSNA were decreased in a single patient 1 year after RDN[170]. Another study reported that RDN slightly decreased MSNA and BP in patients with obesity and hypertension[171]. This finding was taken as evidence that blocking renal afferent pathways may contribute to overall sympathoinhibition and reduced BP[169]. However, other investigators failed to observe sustained inhibition of MSNA after RDN and BP reductions were not associated with reduced MSNA in patients with difficult-to-control hypertension[172]. Whether RDN reduces SNA in non-renal blood vessels and in organs other than the kidneys remains unclear.

In obese dogs, surgical RDN reduced renal tissue noradrenaline concentration by over 96% and almost completely abolished hypertension but did not lower plasma noradrenaline levels or HR, suggesting that sensory afferent signals from the kidneys to the brain may not make an important contribution to increases in sympathetic activity or cardiac autonomic dysfunction of obesity[160]. To directly test the importance of renal sensory afferents in obesity-induced hypertension, we surgically removed all afferent signalling from the kidneys by dorsal root ganglionectomy from T10 to L2 in obese hypertensive dogs[173]. This procedure did not blunt the rise in BP during development of obesity-induced hypertension, indicating that the BP effects of RDN are due to ablation of renal sympathetic efferent fibres rather than sensory afferent nerves. Further studies are needed to assess whether renal afferents contribute to obesity-induced hypertension in humans.

Potential mediators of SNS activation

Multiple factors have been proposed to stimulate SNS activity in obesity. The roles of some of these factors, such as insulin resistance, hyperinsulinaemia, fatty acids and AngII, have previously been discussed and are beyond the scope of this Review[152,154–156,174–178]. However, obesity has also been demonstrated to impair baroreceptor reflexes, activate chemoreceptors in carotid bodies (especially in patients with obstructive sleep apnoea (OSA) and hypoxaemia) and activate the CNS POMC pathway (FIG. 7).

Impaired baroreflexes.—Studies in experimental animals and humans indicate that cardiac and RSNA baroreflex sensitivity is depressed after rapid weight gain and in the setting of long-standing obesity[37,155,179]. In dogs, marked reductions in 24-hour cardiac baroreflex sensitivity and HR variability occurred within a few days of starting an HFD, before appreciable weight gain or large BP increases, although these responses intensified with progressive weight gain and hypertension[179]. Similar results were found in rabbits fed an HFD[155]. The rapid onset of impaired baroreflexes with overfeeding suggests that factors associated with increased caloric intake may contribute to this impairment, but definite mediators have not been identified.

Sustained obesity and hypertension also cause baroreflex dysfunction, which slowly regresses during chronic weight loss in individuals with obesity[180,181]. Increased vascular stiffness associated with chronic obesity-induced hypertension could contribute to impaired baroreflex sensitivity by limiting pressure-induced distension of the arterial wall where baroreceptor sensory endings are located.

In obese dogs, chronic baroreflex activation via electrical stimulation of the carotid sinuses reduced BP, HR and HR variability and restored cardiac baroreflex sensitivity to control levels[160]. By contrast, RDN did not restore baroreflex sensitivity despite abolishing obesity-induced hypertension. These results indicate that reductions in BP cannot fully explain improvements in baroreflex sensitivity in obese dogs as BP was similarly reduced by RDN and chronic baroreflex activation (FIG. 6). Carotid sinus stimulation also decreased plasma noradrenaline concentration, suggesting global sympathoinhibition, whereas RDN did not have this effect. These observations highlight the importance of increased efferent RSNA in mediating obesity-induced hypertension and the capacity of baroreflex activation and RDN to abrogate renal sympathoexcitation[160]. However, they provide no evidence that renal sensory afferent signals to the CNS contribute to chronic sympathetic overactivity in obesity-induced hypertension.

Obstructive sleep apnoea, hypoxaemia and chemoreflexes.—Obesity hypertension is frequently associated with OSA, intermittent nocturnal hypoxia and elevated SNA[174,182]. Carotid body chemoreceptors are believed to have a pivotal role in sympathetic dysregulation in OSA, although other mechanisms may also contribute[183,184]. In patients with OSA, breathing 100% oxygen suppressed chemoreflex activity and reduced SNA, HR and BP[183,185].

Studies in experimental animals suggest that chronic intermittent hypoxia produces sustained increases in SNA and BP[186]. Whether a similar effect occurs in healthy humans is

not clear. Although sympathetic dysregulation during hypoxia occurs in patients with OSA, this effect is generally not seen in healthy individuals with voluntary apnoea[182]. Chemoreflex-induced sympathetic responses to hypoxia are exaggerated in patients with obesity and OSA compared with individuals without obesity exposed to hypoxia[182,183]. Obesity is also associated with a heightened central chemoreflex response to hypercapnia in the absence of coexisting disease[182,183]. The mechanisms that underlie central chemoreflex potentiation in obesity are unclear but may be related to increased leptin production by adipocytes[187].

Although obesity-induced hypertension often occurs in the absence of OSA, the severity of hypertension is exacerbated when OSA coexists with obesity[183,185]. Hypoxaemia may also occur in obesity without OSA. Obese dogs fed an HFD were hypoxaemic but eucapnic and appeared to have tonic activation of carotid chemoreceptors as well as increases in BP and respiratory rate[188]. These changes were attenuated by chronic electrical stimulation of the carotid baroreflex or carotid body denervation. Thus, obesity-induced hypoxaemia may stimulate peripheral chemoreceptors, causing compensatory increases in ventilation and SNA that contribute to hypertension. As obesity adversely affects lung function, hypoxaemia may be more common in individuals with obesity than previously appreciated and may occur in the absence of OSA.

Brain melanocortins.—A key CNS pathway that links adipokines and hormones with BP control is the brain POMC-melanocortin 4 receptor (MC4R) system[6,189,190]. In the ARC and brainstem, POMC-expressing neurons project to second-order neurons involved in BP regulation (for example, in the paraventricular nucleus (PVN)), where their axons release a-melanocyte-stimulating hormone (aMSH), the endogenous ligand for MC4R[191] (FIG. 5a).

The POMC-MC4R system is a major regulator of energy balance. Hyperphagia and increased adiposity lead to stimulation of POMC neurons and MC4R signalling, whereas energy deficits and weight loss reduce signalling in this pathway[191,192]. Disruption of POMC-MC4R signalling causes hyperphagia and is the most common known genetic cause of morbid obesity in children[193,194]. In rats, pharmacological activation of MC4R reduced food intake and body weight but increased BP; these effects were abolished by α/β-adrenergic blockade[195,196]. Conversely, MC4R antagonism in SHRs caused hyperphagia, rapid increases in adiposity, insulin resistance and a reduction in BP[197]. The BP-reducing effects of MC4R blockade are enhanced in SHRs and other models of hypertension that are associated with increased SNA[197]. Mice with genetic disruption of MC4R signalling exhibit early-onset obesity, hyperphagia, insulin resistance, dyslipidaemia and other features of metabolic syndrome but have normal or reduced BP even when fed high-salt diets[198]. Thus, in rodents, MC4R signalling seems to be essential for obesity to increase SNA and BP.

MC4R activation may also increase BP in people with obesity. Compared with control individuals with obesity and intact MC4R signalling, individuals with MC4R deficiency had a lower prevalence of hypertension and reduced noradrenaline excretion despite severe obesity, insulin resistance and dyslipidemia[199,200]. Similar to their effects in rodents, treatment with synthetic MC4R agonists raises BP and HR despite causing weight loss in people with obesity; these effects limit the use of MC4R agonists in the treatment of

obesity[199]. These observations suggest that MC4R stimulation increases BP and that the brain POMC-MC4R system has a key role in stimulating SNA and raising BP in the setting of obesity in humans and rodents.

As discussed above, leptin is a major factor that links increased adiposity with POMC neuronal activation, SNA and increased BP; however, other factors may also activate the CNS POMC-MC4R pathway. In obese Zucker rats, which exhibit defective LepR signalling, CNS blockade of MC4R reduced BP[201] and attenuated the sympathetic response to insulin, suggesting that insulin might also activate POMC neurons[202]. MC4R antagonism also decreased BP by >25 mmHg in SHRs, which have increased SNA but are not obese and do not have high levels of leptin[197]. The BP-increasing effects of the hormones neuronostatin and nesfatin 1, which are elevated in obesity, were diminished[203,204], and hypertension induced by inhibition of NO synthesis was attenuated by MC4R blockade[205]. Moreover, patients with obesity and MC4R mutations showed a substantial reduction in apnoea-induced increases in MSNA compared with control individuals with obesity and intact MC4R signalling[206]. Together, these observations indicate that multiple factors can activate CNS POMC-MC4R signalling to mediate SNS activation and increased BP in obesity.

MC4R is a transmembrane G protein-coupled receptor that is found in greatest abundance in CNS neuronal populations that are important for autonomic regulation, including the NTS, dorsal motor nucleus of the vagus, PVN, lateral hypothalamus and preganglionic sympathetic neurons of the IML[192,207] (FIG. 5a). Little is known about the specific neuronal populations that mediate the chronic cardiovascular effects of MC4R activation. However, evidence suggests that cholinergic preganglionic parasympathetic and sympathetic neuronal MC4R may contribute to elevated BP in obesity[208]. In mice with defective MC4R signalling in the CNS, restoration of MC4R expression on POMC neurons partially restored BP responses to acute stress, suggesting that activation of MC4R might sensitize POMC neurons to other stimuli that influence sympathetic activity[209].

MC4R signals mainly through phosphorylation of cAMP and activation of protein kinase A (PKA)[191]. Other MC4R signalling pathways have been proposed[210], but their physiological significance is uncertain. In rats, injection of anti-brain-derived neurotrophic factor (BDNF) antibody into the CNS blunted the anorexic effect of MC4R activation, suggesting that BDNF may be a downstream effector of MC4R[211]. Other factors that have been postulated to contribute to the appetite-suppressing effects of MC4R include oxytocin, corticotropin-releasing hormone (CRH), and melanin-concentrating hormone (MCH)[191]. Whether these factors mediate the BP effects of MC4R stimulation in obesity is unclear.

Together, the available data suggest that the brain POMC-MC4R system is a major regulator of SNA and BP in obesity, as well as energy expenditure, food intake and other major metabolic functions. The neuronal pathways and downstream mediators of POMC-MC4R activation and how they are altered in obesity are rapidly being established.

Conclusions and perspectives

Excess adiposity, especially when localized in visceral regions and around the kidneys, accounts for 65–75% of the risk of primary hypertension[6,7]. Although the complex pathophysiology of obesity-induced hypertension continues to be intensively investigated, considerable evidence from studies in experimental animals and humans indicates a major role of renal compression due to excess PRF, RSF and VAT squeezing the kidneys; activation of the RAAS; and stimulation of the SNS, which together mediate increased renal sodium reabsorption. Adipokines, including leptin, may also contribute to obesity-induced hypertension by activation of the RAAS and SNS. Although the mechanisms that link obesity to increased SNS activity are not fully elucidated, considerable support exists for roles of several factors, including the leptin-CNS melanocortin system, chemoreceptor activation caused by hypoxia and/or OSA and baroreceptor dysfunction. If increased visceral adiposity and its adverse cardiometabolic effects are maintained over many years, target organ injury and CKD may exacerbate hypertension and cause BP to become resistant to antihypertensive therapies

Interventions that focus on diet, exercise and lifestyle modification can be effective in some patients with obesity-induced hypertension, but the rate of recidivism is high and many patients are unable to maintain enough weight loss to substantially reduce their risk of cardiometabolic and renal diseases. The high prevalence of obesity in many countries and its adverse impact on almost every organ of the body, enormous economic costs and associated stigma have created great demand for effective pharmacological therapies. Although several medicines for obesity have been developed and marketed for clinical use, the creation of drugs that are highly effective in reducing adiposity and have a satisfactory safety profile is challenging. Bariatric surgery rapidly reverses many of the metabolic and cardiovascular effects of obesity but is currently recommended for only a small percentage of patients. For most individuals who are overweight or obese, therapeutic strategies are directed primarily at treating hypertension, metabolic disorders and other adverse consequences of excess adiposity. However, the surge in research on the causes and consequences of obesity in the past two decades and the discovery of novel pathways that regulate food intake, energy expenditure, and cardiometabolic functions provide reasons for optimism that increasingly effective strategies for preventing and treating obesity, and consquently hypertension, will soon be available.

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Lipotoxicity

The toxic effect of lipids that accumulate in non-adipose tissue and cause cellular dysfunction.

Renal sinus fat

(RSF). The adipose tissue that accumulates in the renal sinuses, which are cavities within the kidneys that are occupied by the renal pelvis, renal calyces, blood vessels and nerves.

Perirenal fat

(PRF). Also called the adipose capsule of the kidney. The perirenal fat is a structure located between the renal fascia and renal capsule.

Blood flow reserve

The maximum increase in blood flow above the resting level of blood flow.

Hypoxaemia

The condition of abnormally low oxygen concentration in the blood.

Baroreflex

Often called the baroreceptor reflex. The reflex mechanism by which stretch receptors (baroreceptors), located especially in the carotid sinuses and aortic arch, regulate blood pressure.

Hypercapnia

The condition of excessive carbon dioxide concentration in the blood.

Eucapnic

The condition of having normal carbon dioxide concentration in the blood.

Key points

- Obesity is associated with chronic diseases, including hypertension, which is a major risk factor for chronic kidney disease and cardiovascular diseases such as stroke, myocardial infarction and heart failure.
- Excessive weight gain, especially when associated with visceral obesity, raises blood pressure and is the most important known risk factor for primary (essential) hypertension.
- Abnormal kidney function, which is associated with increased tubular sodium reabsorption, has a key role in initiating obesity-associated hypertension.
- Mechanisms that initiate obesity-induced sodium retention include kidney compression by visceral, perirenal and renal sinus fat, stimulation of the renin-angiotensin-aldosterone system, aldosterone-independent mineralocorticoid receptor activation and activation of the sympathetic nervous system.
- Sympathetic activation in obesity may be mediated by hypoxia, chemoreceptor activation, baroreflex dysfunction and adipokines, including leptin, which activates the central nervous system melanocortin pathway.
- Chronic obesity may gradually amplify hypertension, resulting in resistance to antihypertensive treatment and initiating a pathophysiological cascade of factors that exacerbate target organ injury.

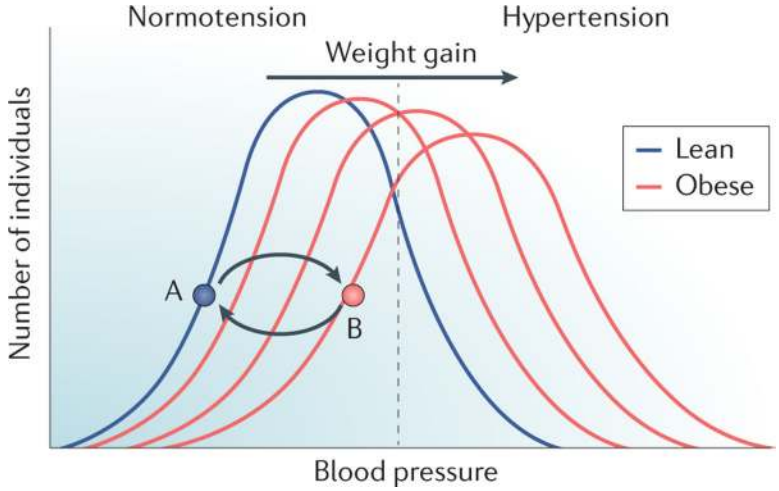

Fig. 1 |. Obesity shifts the frequency distribution of blood pressure.

Not all individuals who are obese have blood pressures in the hypertensive range (>140/90 mmHg); however, obesity raises blood pressure above the baseline level for an individual (for example, from point A to B). Conversely, weight loss lowers blood pressure in individuals who are obese but considered to be normotensive (for example, from point B to A) as well as in those who are obese and hypertensive. Increasing duration of obesity exacerbates the obesity-induced shift of the blood pressure frequency distribution to higher levels of blood pressure.

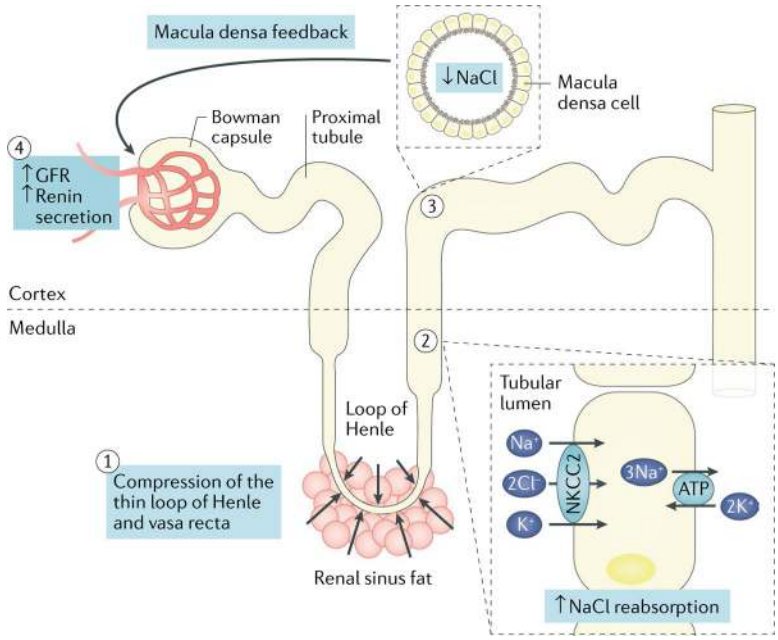

Fig. 2 |. Potential effects of kidney compression on renal haemodynamics, sodium reabsorption and renin secretion.

(1) Increased volumes of renal sinus fat and perirenal fat (not shown) due to obesity might result in compression of the thin loop of Henle and vasa recta of the renal medulla. (2) Such compression would initially result in a reduction in tubular flow rate, increased fractional NaCl reabsorption in the nephron, including in the thick loop of Henle, and (3) a reduction in NaCl concentration at the macula densa cells in the early distal tubule. (4) The reduction in NaCl concentration would, in turn, cause a macula densa feedback-mediated dilation of afferent arterioles, increases in renal blood flow and glomerular filtration rate (GFR) and stimulation of renin secretion from the juxtaglomerular cells of the afferent arterioles.

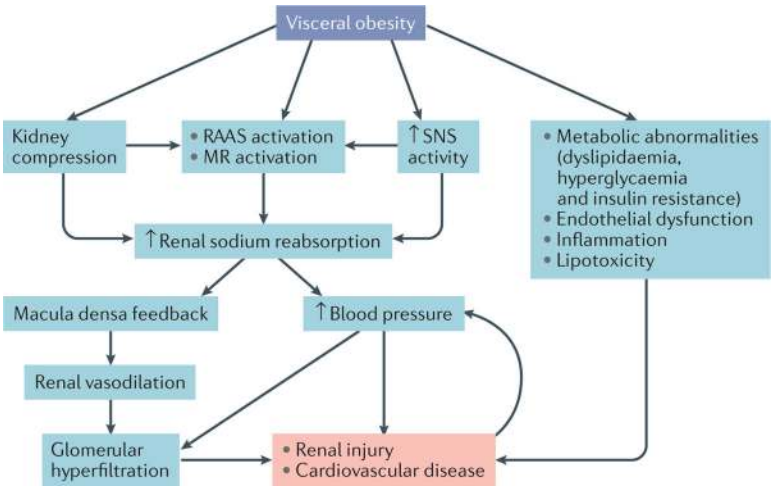

Fig. 3 |. Mechanisms of obesity-induced hypertension, renal injury and cardiovascular disease. Metabolic abnormalities in individuals with obesity may interact synergistically with hypertension to cause renal injury and cardiovascular disease. Increased sympathetic nervous system (SNS) activity stimulates renal tubular sodium reabsorption directly and indirectly by stimulating the release of renin, which activates the renin-angiotensin-aldosterone system (RAAS). Kidney compression may also increase sodium reabsorption in the loop of Henle and contribute to increased renin release and RAAS activation. Activation of the RAAS leads to increased formation of angiotensin II and aldosterone, which both stimulate renal tubular sodium reabsorption. Aldosterone-independent mechanisms may also contribute to renal tubular mineralocorticoid receptor (MR) activation and increased sodium reabsorption. The increased renal sodium reabsorption leads to compensatory renal vasodilation which, in combination with increased blood pressure, initially causes increased glomerular hydrostatic pressure and glomerular hyperfiltration, which may further exacerbate renal injury. As obesity is sustained over many years, progressive renal injury can exacerbate hypertension and lead to resistance to antihypertensive therapies.

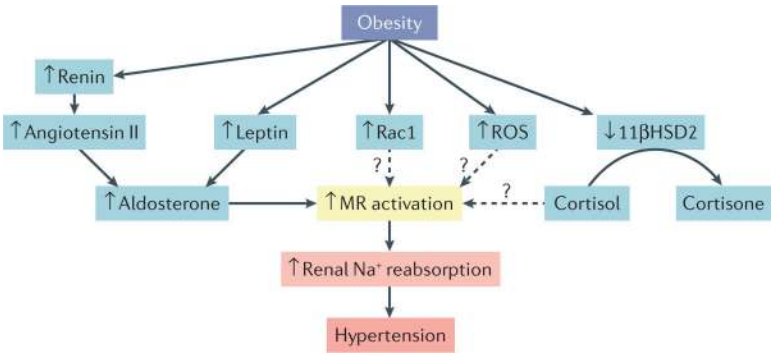

Fig. 4 |. Potential mechanisms and consequences of MR activation in obesity.

Under normal conditions, aldosterone is the primary agonist of the renal tubular mineralocorticoid receptor (MR). Obesity leads to increases in renin secretion and the formation of angiotensin II, which stimulates secretion of aldosterone from the adrenal gland. Leptin has also been suggested to stimulate aldosterone secretion in individuals with obesity. However, obesity might also lead to MR activation via aldosterone-independent mechanisms such as increased renal tubular expression of Racl and increased reactive oxygen species (ROS). Obesity might also enable cortisol-induced activation of the MR by inducing downregulation of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), which converts cortisol to cortisone. In contrast to cortisone, cortisol does not avidly bind the MR. Activation of the MR increases sodium reabsorption in the renal tubules, contributing to expansion of extracellular fluid volume and increased blood pressure in obesity.

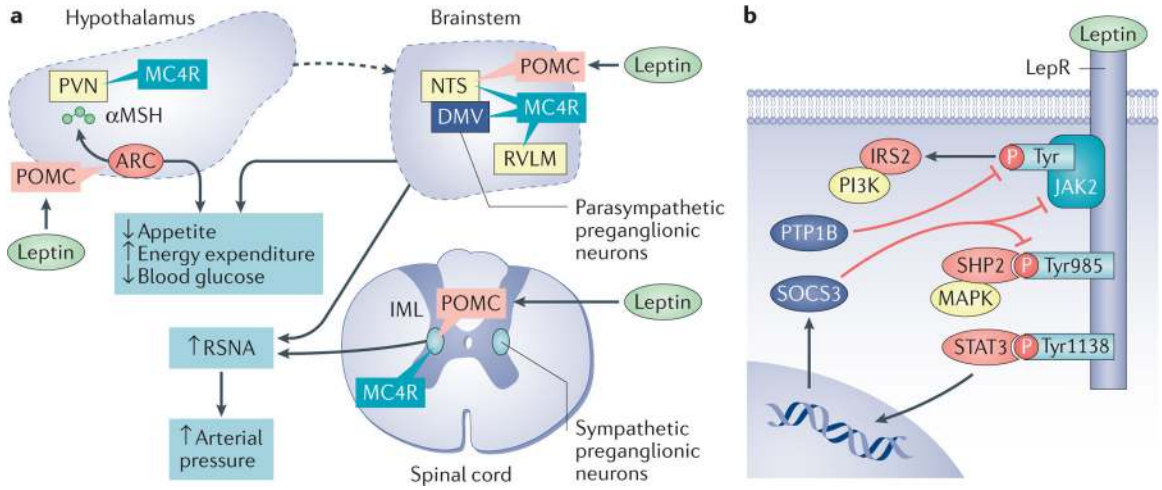

Fig. 5 |. Effects of CNS leptin-melanocortin activation on blood pressure and metabolic functions.

Activation of leptin receptors (LepRs) in different neuronal populations and the resulting activation of three primary intracellular signalling pathways likely contribute to the differential effects of leptin on cardiometabolic functions in obesity, a | Activation of LepRs expressed on proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus (ARC), nucleus tractus solitarius (NTS) of the brainstem and intermediolateral nucleus (IML) of the spinal cord causes release of a-melanocyte-stimulating hormone (aMSH), which stimulates melanocortin 4 receptors (MC4Rs) in second-order neurons of the hypothalamus, brainstem and spinal cord IML. b | Binding of leptin to the LepR activates its associated Janus tyrosine kinase 2 (JAK2) tyrosine kinase, leading to autophosphorylation of tyrosine residues on JAK2 and phosphorylation of Tyr985 and Tyr1138 on the LepR. Autophosphorylation of JAK2 activates insulin receptor substrate 2 (IRS2)-phosphatidylinositol 3-kinase (PI3K) signalling, which contributes to the blood pressure effects of leptin. Phosphorylation of Tyr985 activates Src homology 2 tyrosine phosphatase (SHP2)-mitogen-activated protein kinase (MAPK) signalling, which has an important role in the cardiometabolic actions of leptin. Phosphorylation of Tyr1138 activates signal transducer and activator of transcription 3 (STAT3). In addition to mediating multiple effects of leptin such as reduced food intake and increased blood pressure, STAT3 activation induces transcription of suppressor of cytokine signalling 3 (SOCS3), which binds to phospho-Tyr985 and to the LepR-JAK2 complex and attenuates LepR-mediated signalling. Protein tyrosine phosphatase 1B(PTP1B) also attenuates leptin signalling by dephosphorylating JAK2. CNS, central nervous system; DMV, dorsal motor nucleus of the vagus; PVN, paraventricular nucleus; RSNA, renal sympathetic nerve activity; RVLM, rostral ventrolateral medulla.

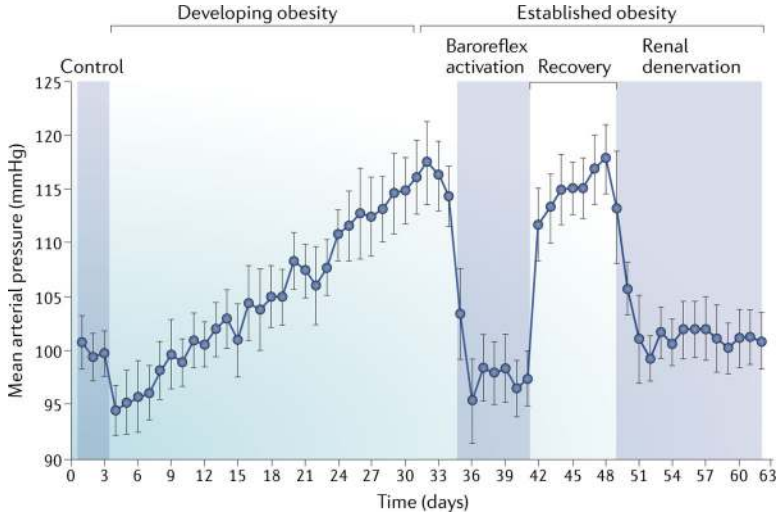

Fig. 6 |. Obesity-induced hypertension and the effects of renal denervation.

During days 4–31, obesity and associated hypertension were induced by feeding dogs supplements of cooked beef fat along with a fixed amount of a prescription diet. During this time, body weight increased by −50%. After day 31, dietary fat supplements were minimal and there were no further changes in body weight during the remainder of the study Chronic baroreflex activation (by electrical stimulation of the carotid sinuses) or bilateral surgical renal denervation normalized blood pressure in dogs with established obesity Values are means ± s.e. from 24-hour recordings of arterial pressure. Adapted with permission from REF.[162], American Physiological Society

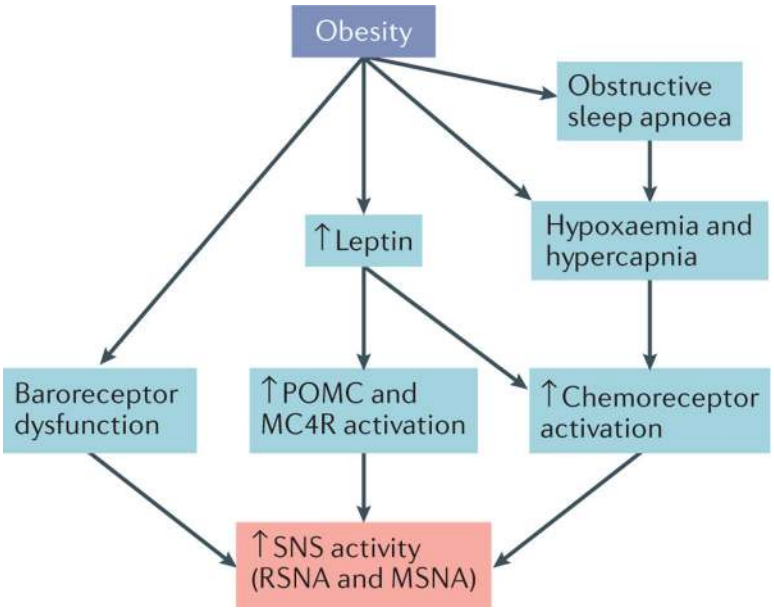

Fig. 7 |. Potential mechanisms of SNS activation in obesity.

As adipocytes grow larger, they secrete increased amounts of leptin, which increases sympathetic nervous system (SNS) activity mainly by stimulating proopiomelanocortin (POMC) neurons. These neurons release a-melanocyte-stimulating hormone, which stimulates melanocortin 4 receptors (MC4Rs) in the hypothalamus and brainstem. Leptin may also enhance the sensitivity of chemoreceptors to hypoxaemia. Obesity may also stimulate SNS activity via hypoxaemia, hypercapnia and chemoreceptor activation secondary to obstructive sleep apnoea and via other mechanisms that are still poorly defined. Obesity is also associated with rapid onset of baroreceptor dysfunction, but the mediators have not yet been elucidated. MSNA, muscle sympathetic nervous system activity; RSNA, renal sympathetic nerve activity.

Table 1 |

Haemodynamic, renal and neurohormonal changes in obesity

Parameter	Humans	Dogs	Rabbits	Rats	Mice	Refs
Haemodynamics						
Arterial pressure	↑	↑	↑	↑ or ↔	↑ or ↔	6,7,35,212–215
Heart rate	↑	↑	↑	↑	↑ or ↔	37,212,213,216–218
Cardiac output	↑	↑	↑	↑	NA	47,213,219,220
Eccentric cardiac hypertrophy	↑	↑	↑	↑	↑	36,221–225
Concentric cardiac hypertrophy	↑	↑	↑	↑	↑	36,221,225,226
Cardiac diastolic function	↓	↓	↓	↓	↓	36,221,223,225,227
Resting muscle blood flow	↑	↑	↑	NA	NA	213,221,228,229
Muscle blood flow reserve	↓	↓	NA	NA	NA	221,228,229
Kidney function						
GFR[a]	↑	↑	↑	↑ or ↔	↑	212,214,230–233
Renal blood flow[a]	↑	↑	↑	↑ or ↔	NA	212,213,230,231,233
Renal Na^+ reabsorption[a]	↑	↑	↑	↑ or ↔	↑ or ↔	212,214,230,232,234,235
Kidney compression	↑	↑	↑	↔	↔	6,19,20,236
Hormonal changes						
Fasting plasma insulin	↑	↑	↑	↑	↑	14,225,226,237–239
Insulin sensitivity	↓	↓	↓	↓	↓	14,225,226,237
Fasting plasma leptin	↑	↑	↑	↑	↑	6,129,214,218,239
Plasma renin:angiotensin II	↑	↑	↑ or ↔	↑ or ↔	↑	212,238,240–242
Plasma aldosterone	↑	↑	↑	↑	↑ or ↔	6,212,235,238,240,241,243
Neural control[b]						
Renal sympathetic activity	↑	↑	↑	↑	↑	155,160,161,163,164,244
Cardiac sympathetic activity	↓ or ↔	NA	NA	NA	NA	152
Muscle sympathetic activity	↑	NA	NA	NA	NA	152,153
Baroreflex sensitivity	↓	↓	↓	↓	↓	6,37,152,155,244,245

GFR, glomerular filtration rate; NA, not available. ↑ increase; ↓ decrease; ↔ no change. Arrows indicate changes in obese compared with lean humans and in animal models of dietary-induced obesity compared with controls fed a normal diet.

[a] Comparisons refer to the early phases of obesity before major loss of nephron function has occurred.

[b] In some instances, sympathetic activity was inferred from indirect measurements such as tissue noradrenaline spillover or from denervation studies.