Obesity, kidney dysfunction, and inflammation: interactions in hypertension

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Abstract

Obesity contributes 65–75% of the risk for human primary (essential) hypertension (HT) which is a major driver of cardiovascular and kidney diseases. Kidney dysfunction, associated with increased renal sodium reabsorption and compensatory glomerular hyperfiltration, plays a key role in initiating obesity-HT and target organ injury. Mediators of kidney dysfunction and increased blood pressure include (i) elevated renal sympathetic nerve activity (RSNA); (ii) increased antinatriuretic hormones such as angiotensin II and aldosterone; (iii) relative deficiency of natriuretic hormones; (iv) renal compression by fat in and around the kidneys; and (v) activation of innate and adaptive immune cells that invade tissues throughout the body, producing inflammatory cytokines/chemokines that contribute to vascular and target organ injury, and exacerbate HT. These neurohormonal, renal, and inflammatory mechanisms of obesity-HT are interdependent. For example, excess adiposity increases the adipocyte-derived cytokine leptin which increases RSNA by stimulating the central nervous system proopiomelanocortin-melanocortin 4 receptor pathway. Excess visceral, perirenal and renal sinus fat compress the kidneys which, along with increased RSNA, contribute to renin–angiotensin–aldosterone system activation, although obesity may also activate mineralocorticoid receptors independent of aldosterone. Prolonged obesity, HT, metabolic abnormalities, and inflammation cause progressive renal injury, making HT more resistant to therapy and often requiring multiple antihypertensive drugs and concurrent treatment of dyslipidaemia, insulin resistance, diabetes, and inflammation. More effective anti-obesity drugs are needed to prevent the cascade of cardiorenal, metabolic, and immune disorders that threaten to overwhelm health care systems as obesity prevalence continues to increase.
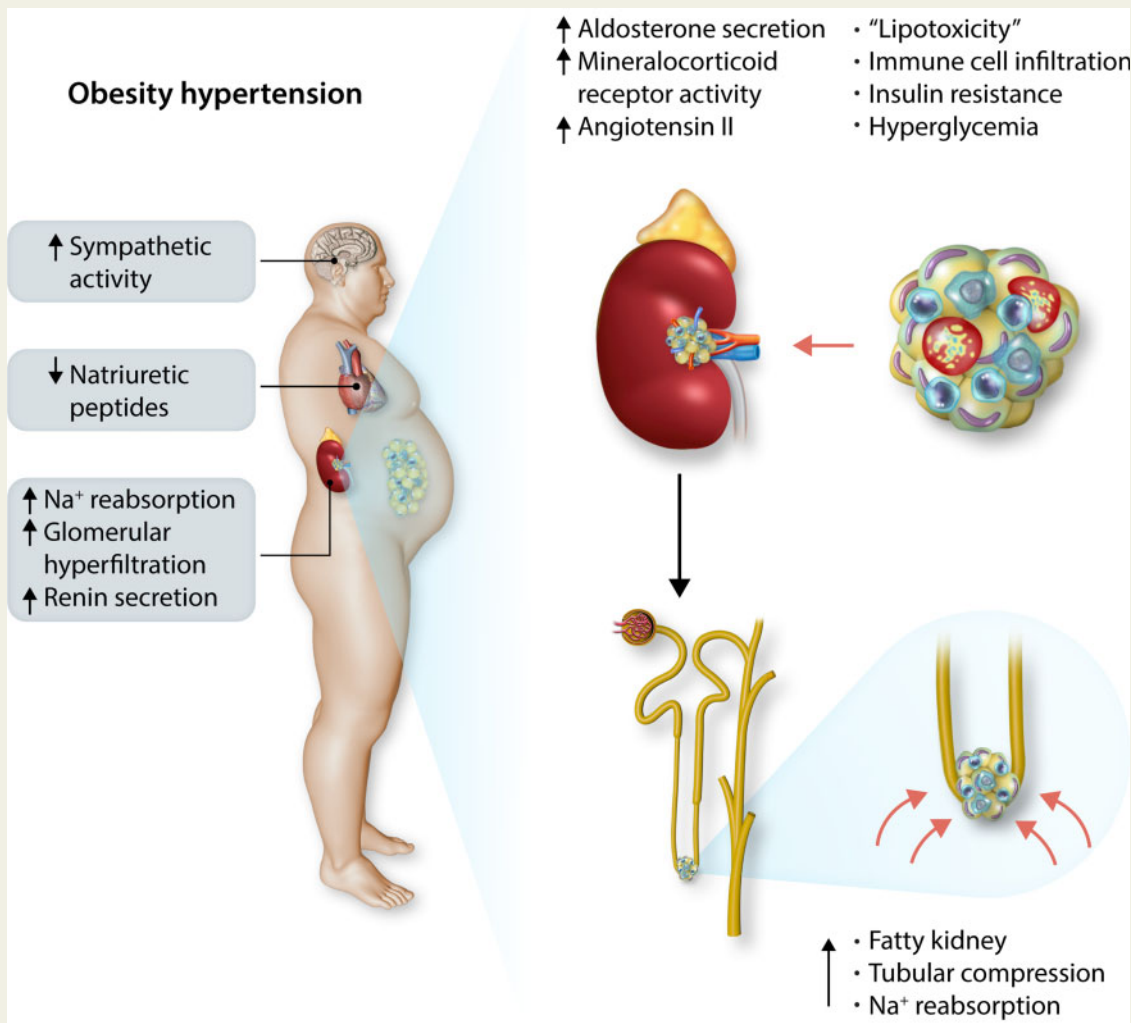
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Graphical Abstract

1. Introduction

The worldwide prevalence of obesity has more than tripled since 1975, with a parallel trend in type 2 diabetes (T2D).[1,2] Over 1.9 *billion* adults were overweight or obese in 2016 and >60% of people with obesity live in developing countries where obesity-associated cardiometabolic disorders, including hypertension (HT), are rapidly increasing.[3] These high rates of obesity will continue growing since >340 million children and adolescents aged 5–19 and >38 million children under the age of 5 are overweight/obese, and obese children usually suffer from obesity as adults. Reasonable projections suggest that nearly 50% of adults in the USA will be obese by 2030[4] and similar trends are forecast for global obesity.

One of the most significant consequences of obesity is HT, a major driver of cardiovascular disease (CVD), stroke and kidney disease. Epidemiology studies indicate that 65–75% of the risk for primary (essential) HT is due to overweight/obesity.[5] At least 72% of patients with end-stage renal disease (ESRD) have HT and/or T2D, both driven largely by obesity. Obesity is also a risk factor for ESRD independent of HT and T2D.[6]

Although obesity is an established cause of HT, the mechanisms involved are multifactorial and not fully understood. However, progress is being made towards elucidating interactions of renal, neurohormonal, and inflammatory factors that link obesity with elevated blood pressure (BP) and end-organ injury. In this review, we highlight key mechanisms that initiate obesity-HT and the potential role of immunity/inflammation and obesity-associated metabolic disorders in exacerbating HT by causing kidney injury.

1.1 Cardiorenal and metabolic risk associated with obesity

Although body mass index (BMI, weight in kg/height in meters[2]) is often used to gauge obesity in clinical studies, BMI does not differentiate

muscle from adipose tissue, or visceral adipose tissue (VAT) from subcutaneous adipose tissue (SAT). Considerable evidence indicates that excess VAT conveys greater risk for insulin resistance, T2D, dyslipidaemia, HT, and cardiorenal disorders than SAT.[7] Thus, individuals with the highest VAT and ectopic fat in organs have higher cardiometabolic risk compared to equally obese subjects with less VAT.[7] Excess fat accumulation in and around the kidneys (renal sinus and perirenal fat) is also associated with HT even after adjusting for overall adiposity, BMI, and other traditional risk factors.[8] Although VAT and BMI are correlated in populations, variations in body fat distribution explain some of the sex, ethnic, and age-related differences reported for associations of HT with BMI.

1.2 Excess adiposity and blood pressure

There is a linear relationship between BP and obesity indices in diverse populations. Approximately 60–76% of overweight/obese subjects have HT, the most common comorbid condition associated with obesity.[9] These estimates are based on HT defined as BP $\geq$ 140/90 mmHg whereas recent guidelines define stage 1 HT as systolic/diastolic BP of 130–139/80–89 mmHg.[10] These new criteria substantially increase the percentage of people with obesity who are considered for HT treatment.

Some people with obesity have BPs not considered as 'hypertensive'. This observation has often been interpreted as evidence that genetic/epigenetic predisposition or other factors are required for obesity to increase BP in some people. However, most studies have not measured VAT, renal sinus fat, and perirenal fat which may be increased in people with HT who have a BMI <30 and are sedentary with sarcopenia. Visceral obesity displaces the BP frequency distribution towards higher pressures, regardless of whether a person's BP resides in the hypertensive range. Thus, weight loss and decreased adiposity in obese people generally reduces BP even when they are 'normotensive'.[8]

Duration of obesity also influences BP. Nyamdorj et al.[11] found in persons 25–74 years old that a 1-SD increase in BMI over a 5-year period led to 30% greater risk of HT compared with people whose weight did not change. In the Nurses' Health Study and the Health Professionals Follow-up Study, weight gain during 10 years of follow-up was associated with higher risk of HT, even for BMIs considered normal.[12] In the Johns Hopkins Precursors Study, obesity in young adults conferred a threefold greater risk of HT at 46 years of follow-up, after accounting for lifestyle changes over the life course.[13] Thus, HT risk increases with increasing obesity duration.

1.2.1 Ethnic and sex differences in hypertension associated with obesity

Although obesity is a major risk factor for HT in all populations that have been studied, the quantitative impact of obesity on BP may depend, at least in part, on age, sex, and ethnicity. In most countries, including the USA, more women than men are obese but a greater percentage of men have HT than women.[14] After menopause, however, HT prevalence in women rises to the same level or higher, compared with men, and comparable increases in BMI cause greater increases in systolic BP in women than in men.[15,16]

Ethnicity also influences the association of obesity and HT. In the USA where the overall prevalence of obesity in adults was 42.4% in 2018, non-Hispanic blacks had the highest age-adjusted prevalence of obesity (49.6%), followed by Hispanics (44.8%), non-Hispanic Whites (42.2%) and non-Hispanic Asians (17.4%).[17] Obesity prevalence was lowest in non-Hispanic Asian women (17.2%) and highest in non-Hispanic black women (56.9%) compared with all other groups.[17] High BP is also more common in non-Hispanic black adults (54%) than in non-Hispanic White adults (46%), non-Hispanic Asian adults (39%), or Hispanic adults (36%).

Differences in body fat distribution among women and men likely explain some of the variations in BMI and BP associations.[18,19] Women generally have greater body fat percentage than men with preferential accumulation of adipose tissue in the gluteofemoral region, whereas men usually have more VAT.[18] Higher levels of oestrogens and lower testosterone in women than men may account for sex differences in VAT before menopause. After menopause, however, increased VAT may be a major driver of increased BP and cardiovascular risk in women as well as in men.

Differences in VAT also have important clinical implications for ethnic/race variations in cardiometabolic risk. Compared with non-Hispanic Whites, Asian Americans have greater VAT and risk for HT and T2D mellitus at lower BMIs.[20–22] These findings have led to recommendations for race/ethnicity-specific cut-offs for waist circumference in the diagnosis of metabolic syndrome.[23] Thus, ethnicity, sex, age, duration of obesity, and location of adipose tissue are all important factors to consider in associating obesity with increased BP and cardiometabolic risk.
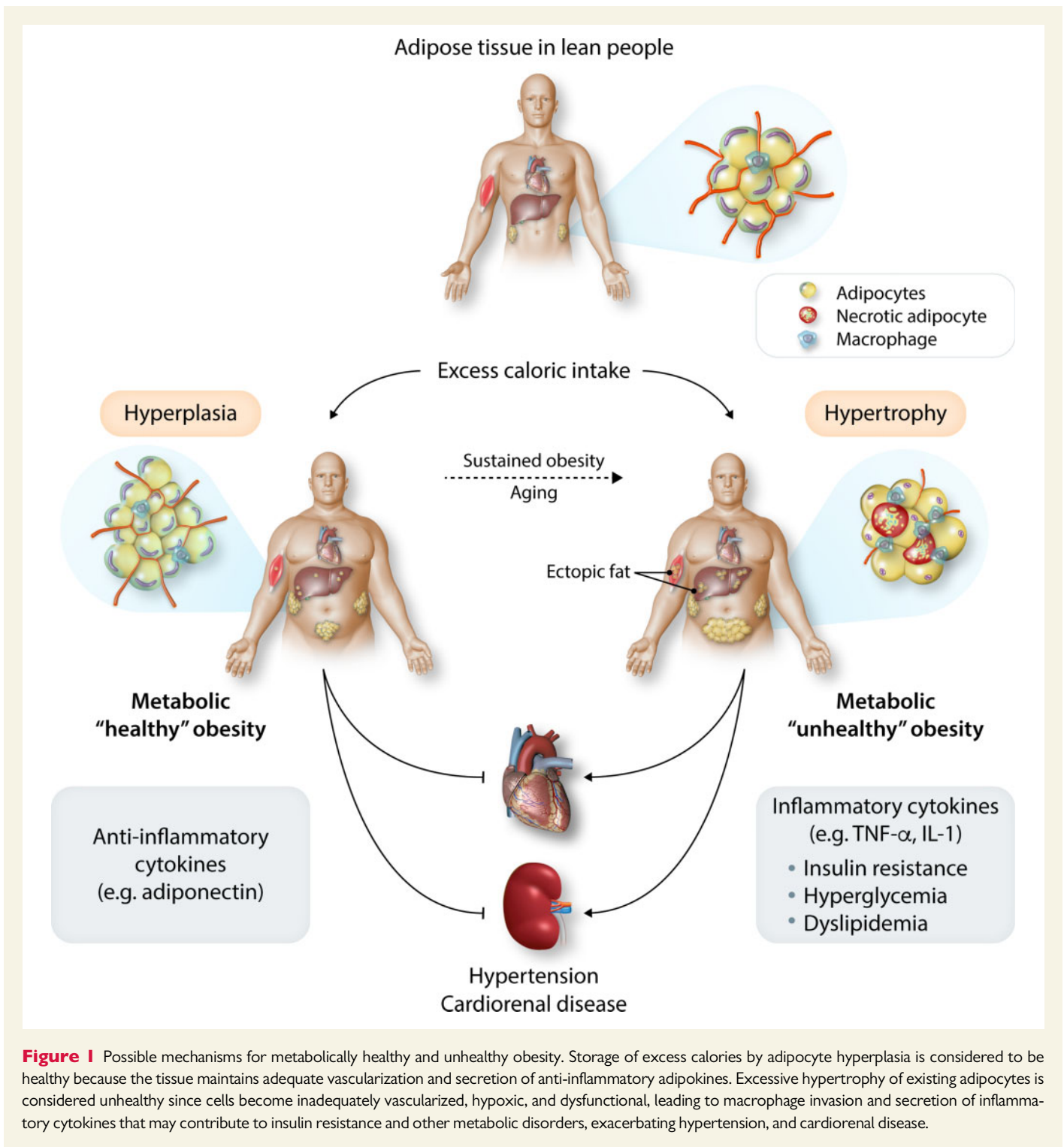
1.2.2 Are some people with obesity 'metabolically healthy'?

Several organizations, including the World Obesity Federation, the Obesity Society, and the American Medical Association, have declared that obesity is a chronic, relapsing progressive disease.[24] Others have proposed the concept of metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) based on clinical observations that a subgroup of people with BMI $\geq$ 30 do not exhibit obvious cardiometabolic abnormalities.[25,26]

Fat location is important in determining cardiometabolic health and accumulation of VAT and ectopic organ fat carries greater risk than SAT.[7,18] Also, whether MHO represents a distinct or stable phenotype is debatable. The Atherosclerosis Risk in Communities study showed that people with MHO had greater increases in BP over a 3-year period compared to normal weight participants.[27] A 30-year follow-up of >90000 women revealed that most obese women who were considered metabolically healthy eventually developed metabolically unhealthy phenotypes associated with increased CVD risk.[28] These and other observations suggest that 'metabolically healthy' obese subjects often convert to unhealthy phenotypes over time.[28]

What causes conversion from MHO to MUO? Increasing the number of small adipocytes (hyperplasia) is considered as a healthy way of storing fat since small adipocytes have adequate supplies of blood and oxygen, normal secretion of the anti-inflammatory hormone adiponectin, and normal insulin sensitivity. In contrast, excessively large, hypertrophied adipocytes have inadequate vascularization, hypoxia, and decreased adiponectin secretion (Figure 1).[29] Some large hypoxic adipocytes may undergo necrosis, causing immune cell infiltration of adipose tissue, inflammation, and insulin resistance. This cascade may ultimately lead to MUO associated with elevated circulating lipids and glucose and ectopic deposition of lipids ('lipotoxicity'), and inflammation in the liver, muscle, heart, kidneys, pancreas, and other tissues.[29,30]

With sustained obesity and ageing, conversion from MHO to MUO may also be related to a gradual decline in adipogenic potential

Figure 1 Possible mechanisms for metabolically healthy and unhealthy obesity. Storage of excess calories by adipocyte hyperplasia is considered to be healthy because the tissue maintains adequate vascularization and secretion of anti-inflammatory adipokines. Excessive hypertrophy of existing adipocytes is considered unhealthy since cells become inadequately vascularized, hypoxic, and dysfunctional, leading to macrophage invasion and secretion of inflammatory cytokines that may contribute to insulin resistance and other metabolic disorders, exacerbating hypertension, and cardiorenal disease.

associated with senescent preadipocytes and decreased capability of SAT to undergo hyperplasia and effectively store lipids.[29] In women, menopause is associated with redistribution of adipose tissue from SAT to VAT and increased ectopic fat accumulation, partly due to loss of oestrogens which promote adipocyte hyperplasia and help prevent excessive enlargement of adipocytes. Excessively hypertrophied adipocytes lead to inflammation, insulin resistance, glucose intolerance, dyslipidaemia, accumulation of ectopic fat, and increased cardiometabolic risk.[31]

2. General mechanisms of obesity-hypertension

The mechanisms that initiate and maintain obesity-HT are complex and time-dependent. Overfeeding rapidly activates the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS), even before large increases in body weight or VAT occur.[30] Conversely, reductions in caloric intake following bariatric surgery cause rapid

reductions in BP, SNS activity and correction of some metabolic disorders before significant weight loss.[32–34]

Activation of the SNS and RAAS in obesity is modest but sufficient to cause increased renal sodium reabsorption, impaired pressure natriuresis, and expansion of extracellular fluid volume. Renal blood flow and glomerular filtration rate are increased (hyperfiltration) in obesity prior to substantial glomerular injury. Blood flows in most other tissues and organs are also elevated in obesity, thereby increasing venous return and cardiac output.[30]

As visceral, perirenal and renal sinus fat accumulate and intra-abdominal pressure increases, the kidneys become compressed, further increasing sodium reabsorption and BP.[8,30] Excessive adipocyte hypertrophy leads to activation of resident macrophages, infiltration of macrophages, and secretion of proinflammatory cytokines that adversely influence kidney function and vascular function throughout the body.[29] When obesity-induced increases in BP, metabolic disorders, and inflammatory mediators coexist and are sustained, gradual injury to end-organs occurs, initiating a cascade that exacerbates HT, making it more resistant to treatment.

3. Sympathetic nervous system activation in obesity

Studies in humans and experimental models indicate that SNS overactivation contributes to initiation and maintenance of obesity-HT.[35,36] Increased sympathetic nerve activity (SNA) in obesity is often mild and non-uniform in various tissues. Muscle SNA (MSNA) and renal SNA (RSNA), assessed by kidney norepinephrine spillover, are higher in obese compared with non-obese normotensive humans.[37] In rabbits RSNA increases within a few days after starting a high-fat diet.[38] In contrast, cardiac norepinephrine spillover may be normal or reduced in obesity-HT, with increased heart rate (HR) due mainly to decreased parasympathetic activity.[37,39]

Age, sex, ethnicity, and differences in fat distribution contribute to variability of SNA and BP among obese subjects. Increased muscle SNA is more closely associated with VAT than with SAT or overall adiposity.[40] Unfortunately, accurate assessments of SNA in various organs in younger and older men and women of different ethnicities are limited and essentially all measurements have been made under quiet, resting conditions which may not reflect SNA during normal daily activities.[41]

Despite mild increases in SNA, sympathetic blockade in obese humans or experimental animals with dietary-induced obesity consistently reduces BP.[8,30] These findings indicate that increased SNA contributes importantly to obesity-HT in experimental animals and humans.

3.1 Renal denervation attenuates obesity-hypertension

Renal nerves mediate much of the BP effects of sympathetic activation in obese subjects. In obese dogs, renal denervation (RDN) greatly attenuated sodium retention and increased BP.[42] RDN also nearly normalized BP in established obesity-HT.[43,44]

In obese humans with resistant HT, catheter-based radiofrequency RDN significantly lowered BP for up to 3 years.[45] However, most clinical trials were confounded by failure to determine the extent of RDN and because patients were already on ≥3 BP medications, including

antagonists of the RAAS which contributes to BP effects of RSNA. In hypertensive patients who were not taking antihypertensive medications, RDN significantly reduced 24-h ambulatory systolic BP at 2–3 months compared to the sham procedure, although RDN adequacy was not verified.[46] These results underestimate BP effects of RDN since catheter-based RDN typically causes <40–50% renal nerve ablation unless nerves in renal segmental arteries are ablated.[44,47]

3.2 Potential mediators of SNS activation in obesity

Several mediators of increased SNS activity in obesity have been proposed.[37,40,48] In this review, we focus on (i) impaired baroreceptor reflexes, (ii) chemoreceptor activation, (iii) activation of the central nervous system (CNS) leptin-proopiomelanocortin (POMC) pathway, (iv) hyperinsulinaemia, and (v) inflammation of hypothalamic and/or brainstem neurons.

3.3 Impaired baroreflexes in obesity-hypertension

Cardiac and RSNA baroreflex sensitivities are reduced in obesity-HT.[38,39,49] Iliescu et al.[49] found decreases in 24-h cardiac baroreflex sensitivity within a few days of starting a high-fat diet in dogs, even before substantial increases in adiposity or BP, although these responses escalated with progressive weight gain and HT. Similar results were found in rabbits fed a high-fat diet.[38]

Obesity also blunts cardiopulmonary reflexes activated by volume expansion. Administration of tacrolimus, an immunosuppressive drug that inhibits calcineurin, production of interleukin-2, and proliferation of T cells, restored renal sympatho-inhibition during acute volume expansion.[50] Whether inflammation-induced attenuation of cardiopulmonary-renal reflexes contributes to obesity-HT is uncertain.

Although the importance of diminished baroreflexes in initiating obesity-HT is uncertain, chronic baroreflex activation, by electrically stimulating the carotid sinuses, restored cardiac baroreflex sensitivity and BP to control levels in obese dogs.[44] Sustained BP reductions during chronic baroreceptor stimulation occurred concurrently with decreases in plasma renin activity and renal sodium reabsorption, highlighting the importance of the renal nerves and renin secretion in obesity-HT. Although RDN also decreased BP to normal levels in obese hypertensive dogs, RDN did not improve baroreflex sensitivity.[44] These results also indicate that BP reductions can be achieved by RDN independently of changes in baroreflex sensitivity in obesity-HT.

Clinical studies also indicate that chronic baroreflex stimulation, electrically or mechanically with an endovascular device, diminishes central sympathetic outflow and reduces BP in patients with treatment-resistant HT.[44] However, randomized, controlled trials have not been completed to demonstrate long-term safety and efficacy of baroreflex activation for treating HT.[44]

3.4 Role of hypoxaemia and chemoreflexes in obesity-hypertension

Obesity-induced hypoxaemia may activate peripheral chemoreceptors, causing increases in SNA that raise BP. Obese dogs were hypoxaemic but eucapnic and appeared to have tonic activation of carotid chemoreceptors associated with increases in BP and respiratory rate.[51] Chronic electrical stimulation of the carotid baroreflex or carotid body denervation attenuated increases in BP and respiratory rate despite worsening

hypoxaemia in obese dogs. Since obesity increases metabolic rate and impairs respiratory mechanics, hypoxaemia may be more common than previously appreciated, even in the absence of obstructive sleep apnoea (OSA).

Obesity-HT is frequently associated with OSA, intermittent nocturnal hypoxia, and elevated SNA.[48,52] Suppression of chemoreflex activity by breathing 100% oxygen reduces SNA, HR, and BP.[53] Chemoreflex-induced sympathetic responses to hypoxia and enhanced central chemoreflex responses to hypercapnia are exaggerated in patients with obesity and OSA.[52,53] The mechanisms underlying central chemoreflex potentiation in obesity are unclear, but may be partly related to increased leptin produced by adipocytes.[54]

The observation that obesity causes chemoreflex activation, even without OSA, has stimulated interest in carotid body resection as a potential treatment for HT although this procedure may worsen hypoxaemia.[55] Currently, studies on the role of peripheral or central chemoreceptors in humans with obesity-HT are scarce and usually related to respiratory rather than BP responses.

3.5 Role of leptin in SNS activation and obesity-hypertension

Leptin, a cytokine secreted by adipocytes, may contribute to obesity-HT.[30] Chronic leptin infusion causes modest, slowly-developing increases in BP in rodents,[56,57] consistent with mild SNS activation that increases renal sodium reabsorption but is insufficient to directly cause vasoconstriction. Leptin's chronic effect on BP in male rats was completely abolished by α/β-adrenergic receptor blockade, suggesting mediation by the SNS.[57] However, in female rodents leptin may also raise BP by stimulating aldosterone secretion.[58]

Inhibition of nitric oxide (NO) synthesis potentiates leptin's BP effects despite decreased food intake and weight loss.[59] Because obesity causes endothelial injury, decreased NO bioavailability, and resistance to leptin's anorexic effects, obesity may enhance leptin's BP effects if SNS activation is preserved, as previously reported.[60]

Leptin receptor (LepR) blockade reduces SNA and BP in obese rabbits, further supporting a potential role of leptin in obesity-HT.[61] Also, ob/ob mice with leptin deficiency have morbid obesity, insulin resistance, hyperinsulinaemia, and dyslipidaemia but are not hypertensive, compared to lean control mice.[62] Moreover, a 3-day leptin infusion increased systolic BP in ob/ob mice notwithstanding substantial weight loss.[63] Thus, leptin contributes to elevated BP in obese rodents. However, leptin is not the only factor driving increased SNA in obesity since obese Zucker rats with defective leptin signalling may have increased sympathetic activity and mild increases in BP, possibly related to impaired baroreflexes as well as activation of the CNS melanocortin pathway.[64,65]

Leptin's role in human obesity-HT is less clear. Intravenous leptin infusion stimulates SNA in humans,[66] similar to findings in rodents. However, subcutaneous injections of recombinant leptin for 12 weeks in overweight/obese humans did not raise BP, although BP was not a primary outcome and leptin had no significant effects on body weight.[67] In a study of four severely obese patients with leptin gene mutations, only one had high BP, possibly due to underlying adrenocorticotrophic hormone excess.[68] Humans with leptin-deficiency also exhibited impaired autonomic function, reduced BP responses to hypertensive stimuli, and decreases in BP and RAAS activation during upright posture. Thus, available data in humans, although limited, suggest that leptin increases SNA and in the absence of leptin, even severe obesity, insulin resistance, hyperinsulinaemia, and dyslipidaemia may not increase BP.

3.5.1 Brain sites of leptin action

Leptin increases SNA and BP by activation of neurons in the hypothalamus and brainstem. After deletion of LepR in the hypothalamic arcuate nucleus (ARC) leptin failed to increase RSNA.[69] Also, deletion of LepR in POMC neurons of the ARC and brainstem completely abolished the chronic effects of leptin to increase BP.[70] Leptin injections into the brainstem nucleus tractus solitarii (NTS) increased RSNA and BP.[60] Thus, leptin's effects on SNA involve hypothalamic and brainstem neuronal populations.[30,71]

3.5.2 Possible 'selective' leptin resistance in obesity

Although obesity attenuates leptin's anorexic effects, stimulation of RSNA by leptin is maintained.[60] The chronic effects of leptin on BP or HR were also preserved in obese rodents fed a high-fat diet whereas leptin-induced anorexia was attenuated.[72] Similar studies in humans, however, have not been reported and the mechanisms that mediate this 'selective' resistance to leptin in obesity are still uncertain.[60]

3.5.3 Molecular pathways for differential effects of leptin on BP and metabolic functions

In the CNS, leptin stimulates janus tyrosine kinase 2 (JAK2) activity and three intracellular signalling pathways.[73] Signal transducers and activators of transcription 3 (STAT3) plays a major role in mediating the effects of leptin on food intake and overall energy balance.[30,35] Insulin receptor substrate 2 (IRS2)-phosphatidylinositol 3-kinase (PI3K) signalling mediates leptin's effects on SNA and BP but is much less important in regulating energy balance.[74] Src homology-2 tyrosine phosphatase (SHP2) signalling in the forebrain appears to be important in controlling food intake, energy balance, blood glucose and BP.[75] Moreover, the effects of leptin on BP and glucose due to forebrain SHP2 signalling are mediated mainly by POMC neurons, although effects on food intake are mediated mainly by other forebrain neurons.[75,76]

It is possible that obesity differentially affects these three pathways, although this hypothesis has not been adequately tested. Also, different neuronal populations may contribute to differential control of cardiovascular and metabolic functions in obesity. For example, POMC neuron activation is essential for leptin's effects on glucose regulation, RSNA and BP, whereas other neurons appear to be more critical for leptin's actions on energy balance. However, interactions of hypothalamic and brainstem neurons, regulation of their signalling pathways, and how selective leptin resistance occurs in obesity have not been fully elucidated.

3.5.4 Can partial leptin reduction be beneficial in obesity-HT?

Leptin antagonism has not been seriously considered for treating HT since this could exacerbate obesity. However, some studies suggest that hyperleptinaemia *per se* causes leptin resistance and that partial leptin reduction may restore leptin sensitivity and, counterintuitively, reduce obesity. Zhao *et al.*[77] showed in obese mice that a leptin neutralizing antibody, restored hypothalamic leptin sensitivity, reduced food intake, increased energy expenditure, and improved insulin sensitivity. This finding, if confirmed in humans, implies that there is an inflection point for leptin concentration, perhaps influenced by obesity-associated metabolic factors, where further increases cause desensitization of hypothalamic neurons, additional weight gain, and worsening metabolic disorders. In this circumstance, partial leptin reduction may restore leptin sensitivity, reduce adiposity, and improve the metabolic profile.

Because chronic hyperleptinaemia also promotes activation of innate and adaptive immunity as well as inflammation,[78] partial leptin reduction may also reduce inflammation which could have additional beneficial effects, as discussed later. This provocative prediction that partial leptin reduction therapies would be beneficial for control of adiposity, glucose, inflammation, and BP will require testing in humans.

3.6 Brain melanocortins contribute to SNS activation in obesity-hypertension

The CNS POMC-melanocortin 4 receptor (MC4R) system regulates energy balance, glucose metabolism, SNS activity and BP among other actions.[8,79,80] Neurons that express POMC are located in the brainstem and ARC and project to second order neurons involved in BP regulation, such as the paraventricular nucleus (PVN), where their axons release α-melanocyte stimulating hormone (α-MSH), the endogenous ligand for MC4R (*Figure* 2).[79,80]

Hyperphagia and increased adiposity stimulate secretion of leptin, insulin and other factors which, in turn, activate POMC neurons and MC4R signalling while energy deficits and weight loss reduce MC4R signalling. Pharmacological activation of MC4R increases BP, an effect abolished by α/β-adrenergic blockade, despite reducing food intake and body weight.[81,82] Conversely, MC4R antagonism or genetic disruption of MC4R causes hyperphagia, increased adiposity, insulin resistance and
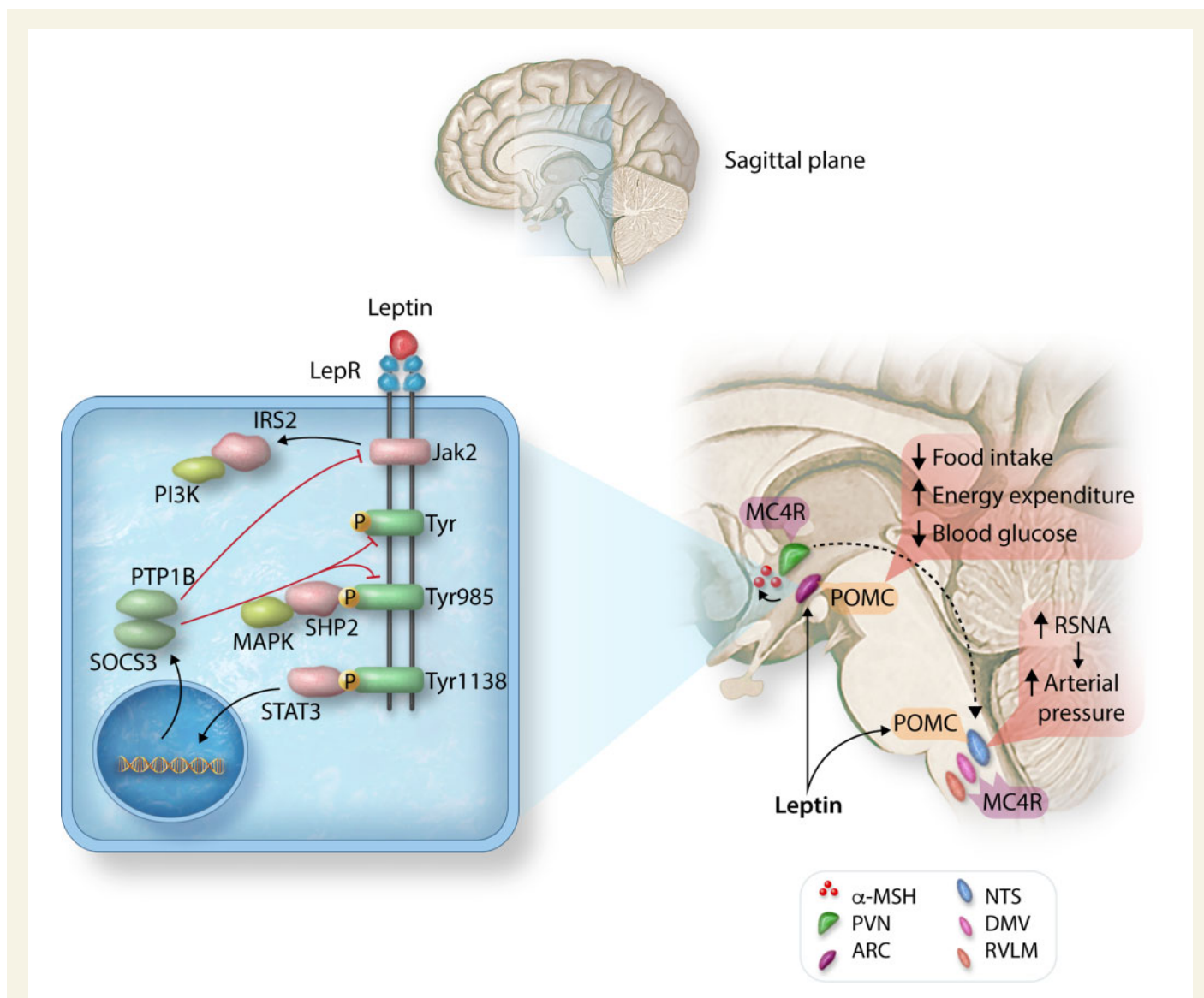
Figure 2 Activation of the CNS leptin-melanocortin system differentially controls food intake, energy expenditure, blood glucose, and arterial pressure by activating distinct signalling pathways in the hypothalamic arcuate nucleus (ARC) and brainstem. Stimulation of leptin receptors (LepR) activates JAK2 tyrosine (Tyr) kinase, causing autophosphorylation of tyrosine residues on JAK2 and phosphorylation of Tyr985 and Tyr1138. Phosphorylation of Tyr985 activates SHP2/MAPK and phosphorylation of Tyr1183 activates STAT3 which mediates several effects of leptin while increasing transcription of SOCS3, which attenuates LepR-mediated signalling. PTP1B is increased in obesity and reduces leptin signalling by dephosphorylation of JAK2. LepR activation of POMC neurons stimulates release of α-MSH, which activates MC4R in neurons in the paraventricular nucleus (PVN), and nucleus tractus solitaries (NTS) and dorsal motor nucleus of the vagus (DMV). ARC, arcuate nucleus; IRS2, insulin receptor substrate 2; RSNA, renal sympathetic nerve activity; and RVLM, rostral ventrolateral medulla.

dyslipidaemia, but normal or reduced BP.[83,84] Thus, in rodents MC4R signalling may be essential for obesity to increase SNA and BP.

Humans with MC4R deficiency are also extremely obese, insulin resistant and dyslipidaemic but have lower prevalence of HT and reduced norepinephrine excretion, compared to control subjects.[85] Similar to results in rodents, treatment of obese people with synthetic MC4R agonists raises BP and HR, effects that have limited use of these drugs for treatment of common obesity.[85] However, MC4R agonists cause reductions in hunger and substantial weight loss in patients with deficiency of POMC or LepR.[86,87] Overall, current evidence suggests that the brain POMC-MC4R system plays a key role not only in body weight regulation but also in stimulating SNA and raising BP in obesity.

3.6.1 Other factors besides leptin activate the POMC-MC4R pathway in obesity

Although leptin is a key link between increased adiposity and POMC-MC4R activation, other factors also activate this pathway in obesity. For example, MC4R blockade reduced BP in obese Zucker rats with defective LepR signalling.[64] MC4R antagonism also markedly decreased BP in spontaneously hypertensive rats (SHR) which are not obese or hyperleptinaemic but have increased SNA.[83] HT associated with inhibition of NO synthesis was also diminished by MC4R blockade[88] and the rise in MSNA during hypoxic stress was reduced in obese humans with MC4R mutations compared to control subjects.[89] These observations indicate that multiple factors can activate CNS POMC-MC4R signalling to mediate SNS activation and increased BP in obesity, and that this system may also be important in regulation of SNA and BP in non-obese subjects.

4. Hormonal mechanisms of obesity-hypertension

Other hormone systems besides leptin also contribute to altered kidney function and increased BP in obesity.

4.1 RAAS activation in obesity-hypertension

The importance of the RAAS in obesity-HT has been previously reviewed[90,91] and is briefly considered in this review. Experimental animals and people with obesity generally have mild increases in most components of the RAAS, including angiotensin II (AngII), and aldosterone.[8,91] RAAS activation occurs despite high BP and sodium retention which normally suppress renin secretion, AngII formation, and aldosterone secretion.

4.1.1 Role of AngII

Although adipocytes produce angiotensinogen, whether they make enough AngII to increase BP in obesity is uncertain. Current evidence suggests that elevated AngII in obesity is driven largely by increased renal renin secretion due to SNS activation, kidney compression, and perhaps other factors.

Despite mild increases in renin and AngII formation, RAAS blockade attenuates sodium retention and obesity-HT.[8] Obesity enhances BP sensitivity to AngII[8,30] and even low levels of AngII stimulate renal sodium reabsorption via direct effects on multiple NaCl transporters and by efferent arteriolar constriction which increases peritubular capillary reabsorption.[91] Constriction of efferent arterioles also raises glomerular

capillary pressure, aggravating the adverse effects of HT on glomerular stress.[91]

RAAS blockade with angiotensin-converting enzyme (ACE) inhibitors or AngII receptor blockers (ARBs) lowers BP effectively in most obese patients with HT.[8,30] While major HT clinical trials have generally included RAAS blockers, randomized trials comparing the effectiveness of RAAS blockers with other antihypertensive agents in lean and obese patients have not been conducted. However, clinical trials have demonstrated that RAAS antagonism attenuates progression of kidney injury in obese patients with HT and T2D.[6,8,30]

4.1.2 Role of aldosterone and mineralocorticoid receptor activation

Although AngII stimulates aldosterone secretion in obesity, leptin may contribute to sex-specific increases in aldosterone secretion. LepR antagonism reduced plasma aldosterone and mineralocorticoid receptor (MR) blockade improved endothelial function in obese female, but not male, mice.[92] Yet, the role of leptin in controlling aldosterone secretion in obese humans, male or female, is still unclear.

Even though there are usually mild increases in plasma aldosterone concentration in obesity-HT, MR blockade reduces BP and end-organ injury. In obese dogs, MR antagonism blunted renal sodium reabsorption, glomerular hyperfiltration, and HT by >50%.[93] MR antagonists also decreased BP in obese patients with treatment-resistant HT although BP reductions did not correlate with plasma aldosterone concentration.[94] Also, spironolactone reduced BP and urinary albumin excretion in obese hypertensive subjects even after blockade of AngII formation.[95]

Compared to other antihypertensive drugs, the MR antagonist spironolactone was superior for treating obese patients with resistant HT who were already on ≥3 antihypertensive medications, usually including an ARB or ACE inhibitor.[96] The antihypertensive benefit of MR blockade appears to be mainly due to reduced renal sodium reabsorption and the resulting natriuresis and diuresis[96,97]

The observation that MR antagonism is effective in reducing BP and protecting against end-organ injury in obesity-HT, despite normal or even reduced plasma aldosterone, suggests that other factors besides aldosterone may activate MR. Several potential mechanisms have been suggested for aldosterone-independent MR activation (*Figure 3*). The GTP-binding protein Rac1, a member of the Rho family of GTPases, stimulates MR signalling and is increased in renal epithelial cells in obesity.[98] Adipocyte-derived cytokines, hyperglycaemia and oxidative stress have been proposed to induce Rac1 expression in obesity.[98] Fujita *et al.*[98] also reported that Rac1 inhibitors ameliorate proteinuria and kidney injury in obesity and in salt-sensitive HT.

Glucocorticoids may also activate MR in obesity if 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is reduced (*Figure 3*). Although cortisol normally has a high affinity for MR, 11β-HSD2 is co-localized with the MR in renal collecting tubules and converts cortisol to cortisone which is relatively inactive at the MR. Supporting the possibility that 11β-HSD2 deficiency may permit glucocorticoids to activate MR in obesity is the finding that renal 11β-HSD2 expression is reduced by 60-70% in obese dogs.[8] Thus, increased oxidative stress, changes in the renal epithelial intracellular redox state, increased Rac1, and decreased 11β-HSD2 could all contribute to MR activation in obesity.[8,99] However, the importance of these factors, in addition to aldosterone, in MR activation in obesity-HT is still unclear.
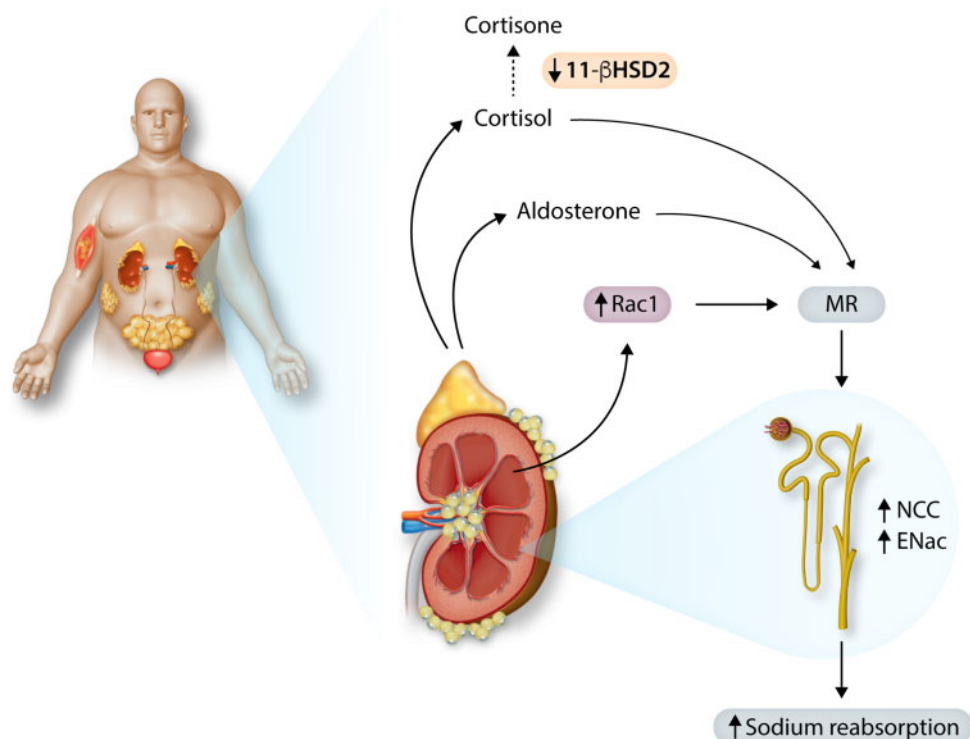
Figure 3 Possible mechanisms of renal tubular mineralocorticoid receptor (MR) activation, increased renal sodium reabsorption, and hypertension in obesity. Obesity increases angiotensin II which stimulates secretion of aldosterone, normally the primary agonist of renal tubular MR. Adipokines, such as leptin, may also stimulate aldosterone secretion and obesity may cause MR activation via aldosterone-independent mechanisms such as increased renal tubular expression of Rac 1, a small GTP-binding protein member of the Rho family of GTPases. Cortisol may also activate MR in obesity via down-regulation of 11β-HSD2, which normally converts cortisol to cortisone, a glucocorticoid that does not avidly bind MR.

4.2 Are natriuretic peptides deficient in obesity-hypertension?

Blood volume expansion and cardiomyocyte stretch normally stimulate secretion of cardiac natriuretic peptides (NP) which circulate to the kidneys, reducing sodium reabsorption and attenuating volume expansion and increased BP. Obese hypertensive men, however, have lower plasma pro-atrial NP levels even though they have higher sodium intake and larger left atria than normotensive lean men.[100] Also, NP responses to volume loading are impaired in obese subjects.[101] Participants in the Framingham Heart Study who were obese had reduced circulating N-terminal pro-atrial NP concentration compared with those with normal BMI,[102] although no significant correlations between BMI and plasma NP concentrations were reported in some other studies.[103]

Since obesity usually causes increased cardiac filling pressures, higher NP secretion is expected. However, a relative NP deficiency in obesity may be due to increased adipocyte-derived neprilysin, an endopeptidase that degrades NP. Obesity may also increase NP receptor-C (NPR-C) a scavenger receptor that facilitates cellular NP uptake and degradation without contributing to increased guanylyl cyclase activity.[104] Thus, higher expression of neprilysin and NPR-C may cause a relative natriuretic handicap in obesity despite increased cardiac filling pressures which would normally stimulate NP secretion. However, the overall significance of abnormal secretion and clearance of NP in obesity-HT is still uncertain.[104,105]

4.3 Role of gut hormones and microbiota in obesity-hypertension

People with obesity often have decreased gut microbiota (GM) diversity along with metabolic disorders such as T2D.[106] Although changes in diet and subsequent weight gain can alter GM, a causal role for GM dysbiosis in obesity has also been suggested by GM transplantation experiments.[107]

Complex interactions among GM, the immune system, inflammation, and vascular dysfunction in the kidneys and brain have been hypothesized for HT.[108] For example, high-salt intake alters GM in mice and *Lactobacillus murinus* administration attenuates BP responses to high salt intake.[109] The BP effects of GM dysbiosis were proposed to be mediated by induction of T helper 17 (TH17) cells and an autoimmune response.[109] In healthy humans, high-salt intake for 2 weeks decreased intestinal survival of *Lactobacillus* and increased BP, although a cause and effect relationship was not established.[109] However, BP reduction in SHR after ACE inhibition reduced mucosal permeability, inflammation, and dysbiosis[110] suggesting that GM changes may be secondary to HT or RAAS activation which contributes to HT in SHR.

GM are the body's only source of short chain fatty acids (SCFA), including acetate, proprionate and butyrate, produced by GM digestion of dietary fibre. The SCFA products of fibre digestion may influence the immune and nervous systems, epithelial cells, and blood vessels and mediate decreased HT risk with consumption of diets rich in fibre.[108]

Although SCFA production offers a reasonable connection between GM and BP regulation, evidence for a causal relationship in obesity-HT is still limited.

Another potential connection between BP regulation and GM is the enteric nervous system (ENS) which influences autonomic nervous system activity in coordination with gut motility.[108] The ENS communicates with the CNS via sympathetic and parasympathetic input and gut hormones. The vagus nerve sends sensory signals to the NTS, a major CNS centre for cardiometabolic regulation. However, the importance of vagal afferent signals, induced by changes in GM, for BP control is uncertain.

Several gut hormones are influenced by GM, or their metabolites, and have various actions that could alter BP.[111] For example, glucagon-like peptide-1 (GLP-1) increases renal sodium excretion while stimulating insulin secretion, increasing insulin sensitivity, and reducing food.[112] Dipeptidyl peptidase-4 inhibitors, which attenuate degradation of GLP-1, as well as GLP-1 agonists slightly reduce BP in obese animals and hypertensive humans with T2D.[111] Gastrin, an enterokine secreted by gastric G-cells, may also promote natriuresis which could reduce BP.[111]

While the possible role of GM metabolites and gut hormones in cardiometabolic regulation has stimulated substantial interest, there is still limited evidence for a major role in obesity-HT or that GM manipulation (e.g. through fecal transplants, antibiotics, or probiotics) has major beneficial effects for HT therapy. However, this research field is rapidly advancing and the multiple effects of GM and their metabolites on nervous, hormonal, and immune systems of the body are consistent with a potential role for cardiometabolic regulation.

5. Obesity, inflammation, and insulin resistance

Immune/inflammatory cells and their interactions with other cells serve as defenses against pathogens and injury, and are important for tissue homeostasis. Immune cells also respond to changes in their nutrient environment and energy supply in various ways, including release of inflammatory cytokines. Some of these cytokines circulate in the blood and influence metabolism in other tissues and in tissues that release them. Infection-related changes in metabolism as well as metabolic/energetic programming of immune responses are recognized as critical components of immunometabolism in adipose tissue and the liver.[113,114] Immunometabolic pathways, including glycolysis and oxidative phosphorylation, are critical for phenotypic switching of various immune cells, and are heavily influenced by obesity-induced metabolic changes such as hyperglycaemia and hyperlipidaemia.[115]

This crosstalk between immune and metabolic systems permits tissues to eliminate pathogens, adapt to changing energy needs, and is essential for tissue repair and remodelling after injury.[114] However, immune-inflammatory responses must be spatially and temporally regulated to maintain homeostasis. If inflammatory responses are excessive or sustained too long, they may damage tissues and cause metabolic derangements.

As discussed previously, excess energy is stored mainly as fat in adipocytes which undergo hypertrophy and hyperplasia. Visceral adipocytes have limited hyperplastic potential and undergo hypertrophy when storing additional lipids. As these cells enlarge, they become inadequately vascularized and hypoxic, leading to cell stress, apoptosis, immune cell infiltration, and increased secretion of inflammatory cytokines (*Figure 4*). As adipocytes become inflamed and dysfunctional, lipids are stored in other tissues such as the liver, skeletal muscle, pancreas, kidneys, and heart leading to 'lipotoxicity' and a cascade of cardiometabolic disorders.

The molecular pathways leading to inflammation and insulin resistance in obesity have been the subject of considerable research and previously reviewed.[29,114] The innate immune system, which is highly regulated by infiltrating and tissue resident macrophages, plays a critical role in adipose tissue inflammation. Obesity is associated with activation and infiltration of macrophages into adipose tissue, especially VAT. Hypertrophied VAT secretes pro-inflammatory cytokines such as IL-1β and TNF-α as well as chemokines that attract circulating monocytes into adipose tissue where they become activated macrophages. The hypoxic environment and exposure to other factors, such hyperglycaemia, impair macrophage and T lymphocyte oxidative metabolism and promote glycolytic metabolism via hypoxia-inducible factor 1α activation, thus polarizing macrophages to a pro-inflammatory M1-like phenotype and T lymphocytes to a pro-inflammatory Th17 phenotype, and causing systemic low grade inflammation.[115] Activation of the inflammasome complex enables maturation of pro-inflammatory cytokines IL-1β and IL-18 and is also an integral part of innate immunity that may contribute to metabolic disorders in obesity.[114]
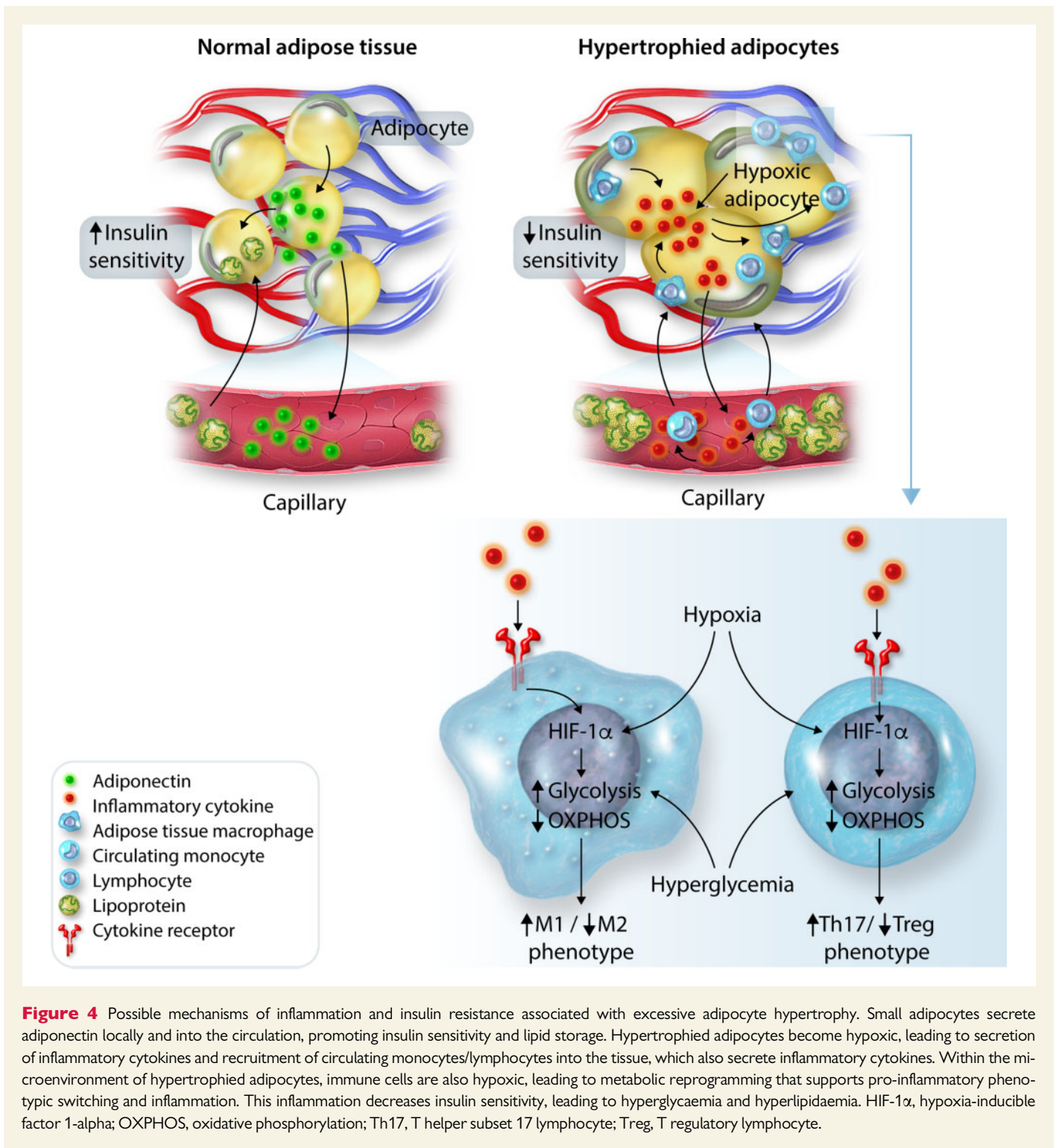
The adaptive immune system also plays a role in adipose tissue dysfunction. There are increases in CD4+ and CD8+ T cells in VAT of obese humans and mice.[116] Conversely, regulatory T (Treg) cells are reduced in VAT of insulin resistant subjects and adoptive transfer of Treg cells improves glucose homeostasis in obese mice.[117] The beneficial effect of Treg cells apparently requires expression of peroxisome proliferator-activated receptor gamma (PPARγ). B lymphocytes also accumulate in VAT of obese mice and produce inflammatory cytokines.[118]

Immune cell-mediated inflammation in VAT, liver, and skeletal muscle has been proposed to play a major role in obesity-associated metabolic disorders, including insulin resistance and T2D.[29,114] Several agents have been used to block specific components of the immune-inflammatory systems, including tumour necrosis factor (TNF)-α, interleukins, Janus kinase enzyme, and T cells. Some studies suggest that these agents reduce risk of insulin resistance and diabetes in patients with chronic inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE).[119] However, there has been limited success in using anti-inflammatory drugs to improve insulin sensitivity and overall metabolic function in obese humans. Challenges in interpreting these results have been previously reviewed.[114,119] In patients with obesity and T2D, anti-inflammatory therapies may not improve insulin sensitivity, except for high doses of salicylate. In clinical trials, anti-inflammatory interventions such as anti-TNFα antibodies, statins, glucocorticoids, and IL1β receptor antagonists, either failed to improve or worsened insulin sensitivity.[119,120]

A moderate level of inflammation in adipocytes appears to be important for maintaining normal adipose tissue function and insulin sensitivity.[121] These observations highlight a beneficial role of inflammation in adipocytes and illustrate the challenge of modulating, temporally and spatially, immune-inflammatory responses as a treatment for metabolic disorders.

5.1 Does inflammation promote hypertension by causing insulin resistance and hyperinsulinaemia?

Evidence that insulin resistance and hyperinsulinaemia, initiated by inflammation or other mechanisms, can cause HT has been

Figure 4 Possible mechanisms of inflammation and insulin resistance associated with excessive adipocyte hypertrophy. Small adipocytes secrete adiponectin locally and into the circulation, promoting insulin sensitivity and lipid storage. Hypertrophied adipocytes become hypoxic, leading to secretion of inflammatory cytokines and recruitment of circulating monocytes/lymphocytes into the tissue, which also secrete inflammatory cytokines. Within the microenvironment of hypertrophied adipocytes, immune cells are also hypoxic, leading to metabolic reprogramming that supports pro-inflammatory phenotypic switching and inflammation. This inflammation decreases insulin sensitivity, leading to hyperglycaemia and hyperlipidaemia. HIF-1α, hypoxia-inducible factor 1-alpha; OXPHOS, oxidative phosphorylation; Th17, T helper subset 17 lymphocyte; Treg, T regulatory lymphocyte.

controversial.[122,123] Acute studies demonstrated that hyperinsulinaemia increases SNS activity and renal sodium retention, effects that could cause HT, if sustained.[122,124] However, chronic studies in dogs and humans indicate that hyperinsulinaemia, caused by insulin infusion or insulinoma, does not elevate BP.[122,124] In fact, insulin infusion in humans and in dogs caused peripheral vasodilation due to its metabolic effects. In rodents, however, hyperinsulinaemia may increase BP modestly,[122,124] raising the possibility that there may be pathophysiologic conditions that

could unmask a hypertensive action of insulin. Yet, multiple studies in other species have failed to find increased BP during chronic hyperinsulinaemia even under pathophysiological conditions of elevated Ang II, increased adrenergic activity, high-salt intake and reduced kidney function.[122,123]

Although insulin resistance attenuates insulin's vasodilator actions, chronic insulin infusion does not raise BP in obese insulin resistance dogs.[122,123] Also, obese humans and rodents with genetic leptin

deficiency or mutations of the POMC-MC4R pathway have severe insulin resistance and hyperinsulinaemia but do not have increases in SNS activity or BP, compared to control subjects.[8,30]

Taken together, these observations do not support the concept that insulin resistance and hyperinsulinaemia, caused by activation the immune-inflammatory system or other mechanisms, initiate obesity-induced HT. However, these findings do not rule out the possibility that that hyperglycaemia, dyslipidaemia, and other metabolic disorders associated with obesity and insulin resistance, may interact with increased BP to mediate cardiorenal injury, exacerbating tissue inflammation and HT initiated by other factors.

5.2 Obesity and hypothalamic inflammation

In addition to causing metabolic disorders via adipose, muscle and liver inflammation, obesity may also cause inflammation of the hypothalamus which plays a key role in regulating energy balance, glucose metabolism, BP, and many other physiological functions. Thaler *et al.*[125] reported that reactive gliosis and markers of neuron injury occurred in ARC of rats and mice after one week of a high-fat diet and in the mediobasal hypothalamus of obese humans, as assessed by magnetic resonance imaging.

Factors that link obesity with hypothalamic inflammation and obesity-induced HT has been largely unexplored. Mechanisms proposed to explain obesity-induced hypothalamic inflammation include cytokines released from adipose or other peripheral tissues, activation of toll-like receptor 4 (TLR4), induction of endoplasmic reticulum (ER) stress, and activation of the inhibitor of nuclear factor-κβ kinase subunit β (IKKβ)/ nuclear factor-κβ (NF-κβ) pathway.[126]

Purkayastha *et al.*[127] showed that constitutive activation of IKK-β (IKK-βCA) and NF-κB in the mediobasal hypothalamus of mice increased BP without altering body weight. They also reported that NF-κB inhibition in the mediobasal hypothalamus attenuated obesity-HT independent of changes in body weight and that POMC neurons appeared to be crucial for the hypertensive effects of hypothalamic IKK-β and NF-κB activation. A potential link between obesity and activation of the NF-κB pathway in POMC neurons is increased TNF-α secreted by activated macrophages in VAT.

Despite evidence that obesity causes inflammation and injury of hypothalamic neurons that regulate BP, there is limited evidence that hypothalamic inflammation drives obesity-HT. If inflammation causes injury to hypothalamic neurons and impairs leptin signalling, how would this cause increased BP if activation of these excitatory neurons is critical for obesity-HT? One possibility is that inflammation may exert time-dependent effects on neuronal activity, initially activating hypothalamic POMC neurons and contributing to increased BP, but eventually causing neuronal injury, reduced sensitivity to leptin, and exacerbation of obesity.

Another possibility is that hypothalamic inflammation may cause 'selective' leptin resistance, whereby leptin's effects to increase SNA and BP are preserved while appetite suppression is attenuated.[60] Two negative regulators of leptin signalling that attenuate leptin's anorexic effect and are influenced by inflammation are suppressor of cytokine signalling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B).[8,30] Activation of NF-κB and hypothalamic inflammation have been suggested to up-regulate SOCS3 and PTP1B, providing a potential mechanism by which hypothalamic inflammation could contribute to feeding dysregulation. Although increased expression of SOCS3 and PTP1B may contribute to the blunted anorexic effects of leptin in obese mice, deletion of SOCS3

or PTP1B signalling in POMC neurons did not significantly alter BP or leptin's chronic effects on BP.[128,129]

In some forms of severe experimental HT, hypothalamic neuronal inflammation may increase BP. For example, Inhibition of NF-κβ in the PVN attenuates AngII-HT by reducing pro-inflammatory cytokines and reactive oxygen species (ROS).[130] Other studies also demonstrated that AngII-HT is associated with increased pro-inflammatory cytokines, ER stress, increased ROS in the PVN, and that blockade of these changes can attenuate increased BP. Yet, it is difficult to extrapolate results from studies in which high doses of Ang II have been infused in rodents to obesity-induced HT or to primary HT in humans. Currently, the role of hypothalamic inflammation in initiating or maintaining obesity-HT is still uncertain.

5.3 Inflammation and obesity-hypertension—which comes first?

Excessive, prolonged activation of immune-inflammatory mechanisms in conditions such as in SLE clearly causes injury to the kidneys, which ultimately leads to HT. Thus, in patients and experimental models of SLE, rheumatoid arthritis, and psoriasis, immunosuppressive drugs attenuated HT.[131,132]

There is also little doubt that many forms of experimental and human HT, including obesity-HT, are associated with increased immune cells and inflammatory mediators in blood vessels, kidneys, and other tissues. Chronic HT due to administration of AngII or deoxycorticosterone acetate plus high-salt intake (DOCA-salt) induces T cell and macrophage accumulation, as well as injury to blood vessels and kidneys.[133,134] Seminal studies by Guzik, Harrison *et al.*[134,135] reported that mice lacking recombination activating gene 1 (Rag1-/- mice), required for maturation and development of T and B cells, are protected from oxidative stress, vascular dysfunction and HT during infusion of AngII, norepinephrine, or DOCA-salt. Adoptive transfer of T cells, but not B cells, restored BP responses in Rag1-/- mice. Recent studies by Seniuk *et al.*,[136] however, reported that AngII-induced HT and end-organ injury were not attenuated in Rag1-/- mice,[136] challenging the concept that T and B lymphocytes are critically involved in AngII-mediated HT. These conflicting observations are especially perplexing since the same Rag1-/- mouse strain and control littermates were used as in the original experiments which demonstrated protection from AngII-HT.

Despite inconsistencies in studies using Rag1-/- mice, there is compelling evidence that immune-inflammatory mechanisms contribute to, or exacerbate, increased BP and cardiorenal injury in several forms of experimental HT.[135,137,138] For example, deletion of Rag 1 attenuated HT and renal injury in Dahl salt-sensitive rats fed a high-salt diet.[139] Genetic deletion or pharmacological inhibition of interleukin-17A also decreases BP as well as renal and vascular damage in mice infused with AngII. Genetic deletion or pharmacological inhibition of IL-21, produced by Th17 cells, also attenuated HT and end-organ damage in Ang II-HT.[138] However, most of these studies used lean animals, and whether inflammation contributes to obesity-HT in the same manner is intriguing but uncertain.

5.3.1 Role of increased blood pressure in causing immune cell activation and inflammation

Activation of immune/inflammatory pathways may occur secondary to HT and pressure-induced tissue damage. For example, in Dahl salt sensitive rats, kidney infiltration of ED1+ macrophages and monocytes and tissue damage were greatly attenuated when renal perfusion

pressure was servo-controlled and prevented from increasing during development of HT induced by feeding a high-salt diet.[140] After 7 days of high-salt intake, the numbers of total CD3+ T cells, CD4+ TH cells and CD8+ cytotoxic T cells were all lower in servo-controlled kidneys than in kidneys in which renal perfusion pressure was permitted to increase as HT developed. Also, CD45R+ B cells, CD11b/c+ monocytes, macrophages, and histological injury were increased in kidneys with elevated BP, compared to servo-controlled kidneys which were protected from injury. Other studies indicate that mechanical stretch of endothelial cells promotes monocyte differentiation associated with reduced NO and increased release of IL-6 and hydrogen peroxide.[141]

Thus, increased BP and excessive mechanical stretch promote vascular and renal injury, cytokine release, and infiltration of immune cells which can exacerbate tissue damage. Tissue injury may stimulate formation or presentation of antigens/neoantigens that subsequently trigger an immune response, infiltration of macrophages and T lymphocytes that stimulate release of inflammatory mediators.

The mechanisms by which infiltrating immune cells in the kidneys exacerbate HT are uncertain. Multiple effects of cytokines and ROS released by immune cells have been suggested, including increased tubular sodium reabsorption, increased vascular resistance, and reduced glomerular filtration rate, and ultimately loss of nephrons due tissue injury.[135,137,142]

HT and metabolic disorders associated with obesity clearly contribute to cardiorenal injury which, in turn, can initiate immune responses and inflammation. These responses are critical for repair and remodelling of damaged tissues but sustained, excessive immune activation and inflammation may exacerbate kidney injury and amplify HT severity (*Figure 5*).

5.4 Targeting immune/inflammatory mechanisms as a strategy for treating obesity-hypertension?

Although low-grade inflammation occurs in many forms of HT, anti-inflammatory therapies have not yet proved to be efficacious for reducing BP in obesity-HT or primary human HT.[143] In fact, some anti-inflammatory therapies (non-steroidal anti-inflammatory drugs), and some immunosuppressive therapies may raise BP and exacerbate cardiorenal injury. The impact of immune modulators and anti-inflammatory drugs on BP and target organ injury may depend on when the drugs are administered during the evolution of HT and tissue injury.[143,144]

Although considerable evidence indicates that immune cells and inflammation are involved in HT-associated vascular injury and target organ damage, their role in human primary HT remains unclear. The discrepancies found in various experimental models and the paucity of clinical evidence linking altered inflammation and immune function to primary HT emphasize the importance of further research before firm conclusions can be made regarding the question of whether inflammation precedes or follows HT, and if targeting the immune-inflammatory systems might be beneficial in obesity-HT.

## 6. Obesity and salt-sensitivity of blood pressure

Obesity is often associated with increased salt intake[145] which could contribute to HT in salt-sensitive subjects.[146] Although many consider obesity a salt-sensitive form of HT, BP may not be highly sensitive to short-term changes in sodium intake in some people with obesity. For example, increasing sodium intake 2.5-fold for 5 days was associated with unchanged BP in a small number of patients with severe obesity and average ages of 39–43 years.[147] Egan *et al.*[148,149] also reported that BP was not salt-sensitive in obese patients <45 years old when sodium intake was increased from 20 to 200 mmol/day for 1 week. In contrast, Rocchini *et al.*[150] found that obese adolescents were salt-sensitive compared with non-obese adolescents during successive 2-week periods of high (>250 mmol/day) and low sodium (<30mmol/day) diets; after a 20-week weight loss program, 70% of the subjects who lost more than 1 kg of weight had reduced salt-sensitivity while in the remaining subjects BP was still salt-sensitive. In obese postmenopausal women, moderate sodium restriction caused dramatic reduction in BP (~16 mmHg in systolic BP).[151] In larger clinical trials, sodium restriction reduced BP, albeit modestly and with significant variability, in obese individuals.[152,153]

These differences in salt-sensitivity are perhaps predictable, considering the multiple factors that determine BP response to changes in sodium intake and the different protocols used to assess this phenotype. Salt-sensitivity of BP is a continuous, rather than bimodal, phenotype and varies with aging, loss of functional nephrons, inability to appropriately modulate the RAAS, inflammation, duration of high salt intake, and other factors.[146] With progressive nephron loss, especially in older patients with long-term obesity and onset of T2D, BP becomes more salt-sensitive and the BP effects of weight loss and decreased sodium intake are partly additive. For example, in obese men and women aged 60–80 years, combining weight loss with sodium restriction decreased the hazard ratio for combined outcomes (HT, use of antihypertensive medications, or adverse cardiovascular events) significantly more than did weight loss or decreased sodium intake alone.[154] Moderating salt intake also increases the antihypertensive efficacy of RAAS blockers, similar to the effect of adding a thiazide diuretic to an ACE inhibitor or ARB.[155] Since many obese patients with HT are treated with RAAS blockers which also increase salt-sensitivity of BP, moderating salt intake often facilitates effective control of BP.

7. Progression of chronic kidney injury and resistant hypertension in obesity

Although excessive weight gain and increased adiposity initially cause modest increases in BP, obesity-induced metabolic and inflammatory disorders interact with HT to promote gradual injury to blood vessels and various organs, including the heart and kidneys.[6,120,156,157] The impact of obesity on chronic kidney disease (CKD) is especially apparent when considering that T2D and HT, which are driven largely by obesity, account for at least 70–75% of ESRD. Although rarely considered a distinct cause of CKD, obesity is also an independent risk factor for CKD beyond its effects to cause HT and T2D.[6] In 320 252 adults followed for 15–35 years, ESRD increased progressively as BMI rose even after adjustment for BP, diabetes, smoking, age, and several other variables.[158] Similar results were obtained in a study of more than 100 000 individuals in Japan where the risk for incident ESRD rose for those with a BMI >25 kg/m^2 even after adjusting for confounders such as age, sex, HT, and proteinuria. Reductions in estimated glomerular filtration rate and CKD were associated with higher BMI and waist circumference in 6500 non-diabetic participants[159] and higher risk of renal insufficiency was associated with abdominal obesity in patients with essential HT after adjustment for dyslipidaemia, and hyperglycaemia. Thus, studies in
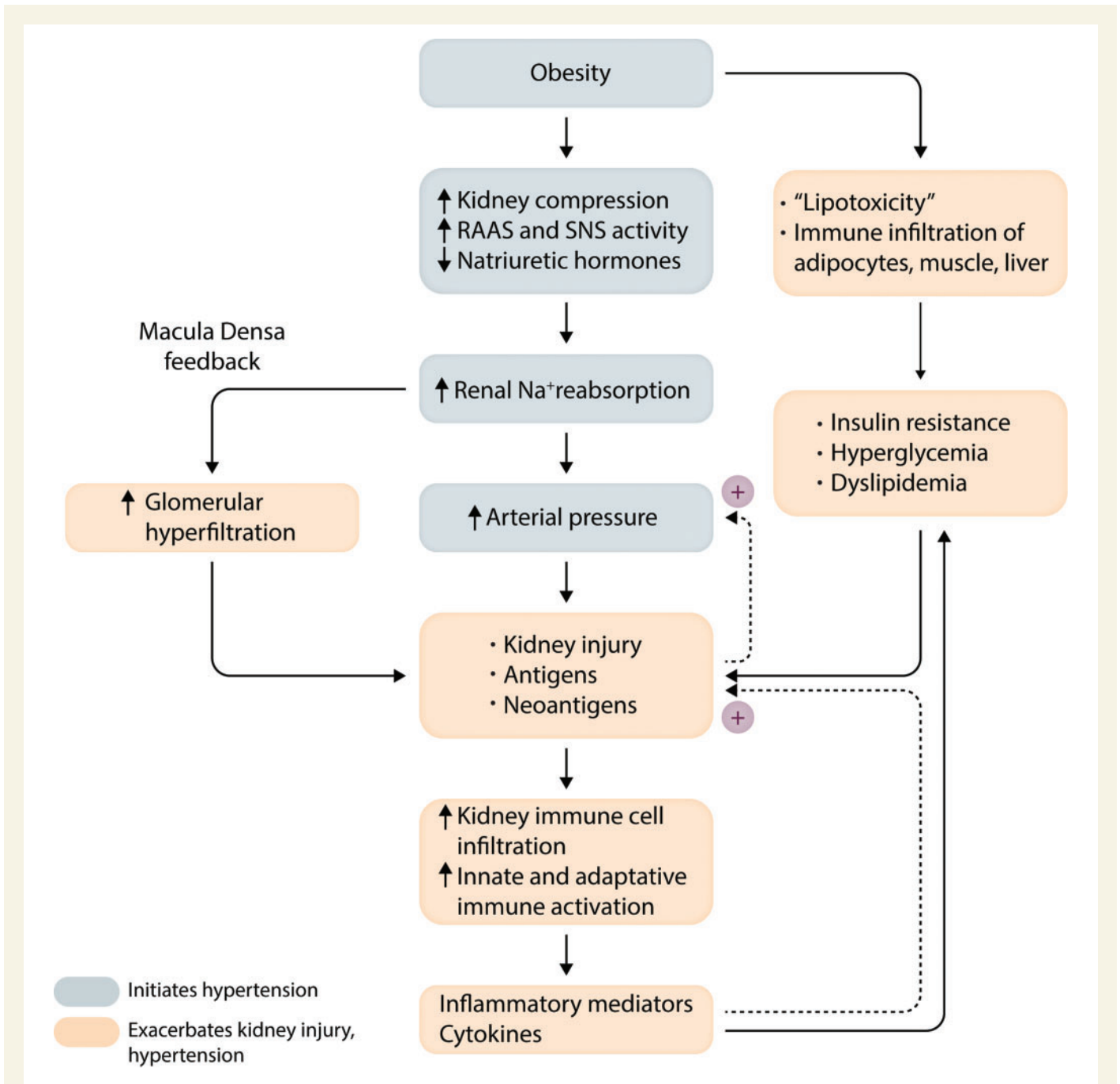
Figure 5 Summary of mechanisms by which obesity initiates development of hypertension and renal injury. Metabolic abnormalities interact synergistically with hypertension to cause renal injury which, in turn, may expose antigens/neoantigens and activate immune/inflammatory mechanisms that exacerbate kidney injury and hypertension. SNS, Sympathetic nervous system; RAAS, renin–angiotensin–aldosterone system.

different populations indicate that kidney disease risk is closely associated with increased BMI and abdominal obesity even after adjustment for other known risk factors.

Early in obesity development, there is microalbuminuria, interstitial fibrosis, increased mesangial matrix, glomerulomegaly, focal glomerulosclerosis, and podocyte abnormalities associated with glomerular hyperfiltration.[160–162] When obesity-HT and metabolic abnormalities are maintained over several years, gradual nephron loss eventually reduces overall glomerular filtration rate despite continuing

hyperfiltration and increased glomerular pressure in surviving nephrons.[6] Nephron loss also increases salt-sensitivity of BP.[146,162] In patients with kidney injury caused by other insults (e.g. unilateral nephrectomy, unilateral renal agenesis, and immunoglobulin A nephropathy), obesity accelerates CKD.[161,162]

Although the multiple factors that mediate obesity-induced kidney damage, in addition to HT and T2D, are still uncertain, several mechanisms have been proposed including mitochondrial dysfunction, oxidative stress, inflammation, dyslipidaemia and 'lipotoxicity' caused by fat

infiltration into and around the kidneys.[162] As discussed previously, these mechanisms are closely interrelated. Hypertrophied adipose tissue is a source of adipokines and inflammatory mediators that may have important effects on kidney function and BP. Elevated BP, interacting with metabolic disorders, contributes to kidney injury which activates immune/inflammatory mechanisms that exacerbate HT and kidney injury, leading to gradual declines in kidney function and treatment resistant HT (*Figure 5*).[163]

Weight loss, whether achieved by lifestyle modification or bariatric surgery, causes rapid remission of major risk factors for CKD, including HT, T2D, dyslipidaemia, inflammation, glomerular hyperfiltration, and proteinuria.[6,33,164] The Action for Health in Diabetes (Look AHEAD) trial, which randomized 5145 obese patients with T2D and mainly normal baseline kidney function to intensive lifestyle intervention or usual care,[165] found that an average weight loss of only 4 kg was associated with a 31% reduction of developing high-risk CKD over an 8-year follow-up period. Multiple studies have shown that Roux-en-Y gastric bypass or sleeve gastrectomy produces more robust and sustainable reductions in adiposity, compared to lifestyle interventions, and rapidly reduces BP, albumin excretion, and other risk factors for CKD.[33] Although these surgical procedures slow CKD progression in diabetic or non-diabetic patients with severe obesity, there are few randomized controlled trials that have included sufficient numbers of patients with pre-existing CKD and statistical power to detect differences in hard outcomes (e.g. ESRD, hospitalization, death). Also, whether weight loss with bariatric surgery can reverse CKD or delay ESRD progression when kidney injury is severe is uncertain. Large, randomized prospective studies with longer follow-up are needed to address these questions.

8. Summary and perspectives

Excess adiposity, especially when associated with increased VAT and ectopic fat, are major causes of HT and target organ injury, contributing 65–75% of the risk for primary HT and >75% of ESRD. Obesity-HT is initiated by increased renal sodium reabsorption and attenuated renal-pressure natriuresis due to moderate increases in RAAS and SNS activity, as well as kidney compression by perirenal and renal sinus fat (*Figure 5*). Obesity-associated inflammation and metabolic disorders interact with elevated BP to exacerbate kidney damage, making HT more severe and resistance to therapy.

For many obese patients, therapy is directed primarily at treating HT, dyslipidaemia, insulin resistance and diabetes, although evidence-based guidelines for effective management of obesity-HT have not been developed. This treatment approach is costly, with many patients on three or more drugs to control BP as well as multiple drugs to manage their metabolic disorders.

The most important therapeutic goal for patients with obesity-HT should be to improve their physical fitness and more effectively manage their underlying causes of obesity. Unfortunately, most obese patients are unable to adequately reduce body weight and adiposity through lifestyle modifications. Also, there are currently few drugs available that can be used to safely and cost-effectively produce sufficient long-term weight loss. A major challenge for developing effective treatment is understanding the complex interplay of behavioural, genetic and physiological factors that influence energy balance and lead to obesity.

Despite rapid advances in obesity-related research in recent years and discovery of many adipokines, hormones, and nervous system pathways that regulate food intake and energy expenditure, development of safe and effective anti-obesity drugs has been challenging. Several relatively new anti-obesity drugs are available for clinical use, but they are often expensive, only moderately effective, and some have challenging safety profiles. The most powerful potential targets for reducing adiposity, such as leptin and the CNS melanocortin system, tend to raise HR and BP when activated. Bariatric surgery, sometimes called 'cardiometabolic surgery' because of its effectiveness in rapidly reversing cardiovascular and metabolic disorders, is an option but is currently recommended for only a small percentage of obese patients. Additional research will be required to better understand the complex physiology that links metabolic and cardiovascular regulation, but the rapid progress occurring in this field is promising and suggests that more efficacious therapies for obesity and the accompanying cascade of inflammatory, metabolic and cardiorenal disorders will be forthcoming.

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