

Obesity-related hypertension: possible pathophysiological mechanisms

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Abstract

Hypertension is one of the major risk factors of cardiovascular diseases, but despite a century of clinical and basic research, the discrete etiology of this disease is still not fully understood. The same is true for obesity, which is recognized as a major global epidemic health problem nowadays. Obesity is associated with an increasing prevalence of the metabolic syndrome, a cluster of risk factors including hypertension, abdominal obesity, dyslipidemia, and hyperglycemia. Epidemiological studies have shown that excess weight gain predicts future development of hypertension, and the relationship between BMI and blood pressure (BP) appears to be almost linear in different populations. There is no doubt that obesity-related hypertension is a multifactorial and polygenic trait, and multiple potential pathogenetic mechanisms probably contribute to the development of higher BP in obese humans. These include hyperinsulinemia, activation of the renin–angiotensin–aldosterone system, sympathetic nervous system stimulation, abnormal levels of certain adipokines such as leptin, or cytokines acting at the vascular endothelial level. Moreover, some genetic and epigenetic mechanisms are also in play. Although the full manifestation of both hypertension and obesity occurs predominantly in adulthood, their roots can be traced back to early ontogeny. The detailed knowledge of alterations occurring in the organism of experimental animals during particular critical periods (developmental windows) could help to solve this phenomenon in humans and might facilitate the age-specific prevention of human obesity-related hypertension. In addition, better understanding of particular pathophysiological mechanisms might be useful in so-called personalized medicine.

Key Words

- ▶ obesity
- ▶ hypertension
- ▶ sympathetic nervous system
- ▶ renin–angiotensin system
- ▶ critical developmental periods
- ▶ epigenetics
- ▶ rat

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Introduction

There is no doubt that the prevalence of obesity and the associated cardiovascular diseases has increased dramatically around the world in the last decade. Current assessment indicates that more than one billion people in the world are overweight or obese (Yach *et al.* 2006,

Aguilera *et al.* 2013). It is estimated that the annual medical burden of obesity and obesity-related diseases costs hundreds of billions of US dollars in the United States alone (Landsberg *et al.* 2013) and this trend has an increasing tendency. International studies on the

economic costs of obesity have shown that they account for 2–7% of total health care costs, the level of which depends on the way the analysis is performed (WHO 2000).

Although the relationship between obesity and hypertension is widely recognized, there is a question as to what is the primary abnormality? It has been suggested that obesity is characterized by a cascade of metabolic and cardiovascular disorders, including hypertension, which is a primary risk factor of obesity-induced cardiovascular disease. Epidemiological studies have demonstrated that overweight predicts future development of hypertension, and the relationship between BMI and blood pressure (BP) appears to be almost linear in different populations (Hall 2003). It seems that this relation exists already at the age of 8–11 years (Falaschetti *et al.* 2010). According to Third National Health and Nutrition Survey (NHANES III), the risk of hypertension has significantly increased in men and women with overweight and it was much higher for subjects with obesity (Must *et al.* 1999). The data from 30 years of follow-up of the original Framingham Study have demonstrated that obesity is an additional independent cardiovascular risk factor to BP (Stokes *et al.* 1989). Moreover, recently, it has been shown that obesity is one of the major determinants of hypertension in the general population (Kannel 2000). A similar conclusion was obtained in the Tecumseh Study (Julius *et al.* 2000), where BP, waist/hip ratio, and plasma insulin were elevated to a higher extent in the hypertensive group. The authors proposed a plausible hypothesis that the weight gain and BP elevation may be intermediate phenotypes of an underlying sympathetic overactivity in hypertension. The association between the family history of essential hypertension and body weight gain was documented by Allemann *et al.* (2001). Healthy normotensive 25-year-old age- and sex-matched male offspring of hypertensive parents were matched for BP with those of normotensive parents. Five years later, the resting BP was still the same in both groups but body weight, BMI, and waist/hip ratio increased more in the offspring of hypertensive parents. The familial predisposition to hypertension and greater body weight gain is also supported by the fact that lean subjects with hypertension are about 2–3 kg heavier than age- and sex-matched normotensives, suggesting a link between the mechanisms that elevate BP and those that stimulate food consumption or lower energy expenditure.

The first explanation of basic mechanisms involved in the relation between human obesity and hypertension was published by Vague (1956). He noted that cardiovascular and metabolic complications of obesity were more common in patients with 'android' type of obesity (upper body

obesity) when compared with 'gynoid' type (lower body obesity). Later on, several studies demonstrated the association of android (or central) obesity, hypertension, and insulin resistance, which formed the basis for understanding the pathophysiology of obesity-related hypertension (Kissebah *et al.* 1982, Kalkhoff *et al.* 1983, Modan *et al.* 1985, for review see Landsberg *et al.* (2013)).

Most recent clinical studies on the morbidities of obesity indicate that the excess weight gain by fat accumulation is not necessarily a determinant for the development of obesity-related diseases, but the abnormal body fat distribution is a more important factor for the morbidity (Matsuzawa *et al.* 2011, Di Chiara *et al.* 2012). Visceral adiposity may have a major role in the occurrence of hypertension, diabetes mellitus, hyperlipidemia, and atherosclerosis not only in obese humans but also in animal models of diet-induced obesity (Davy & Orr 2009, Hall *et al.* 2010). Recent evidence revealed several biological and genetic differences between intra-abdominal visceral fat and peripheral subcutaneous fat. Such differences are also reflected in their contrasting roles in the pathogenesis of obesity-related cardiometabolic problems (Hamdy *et al.* 2006). The functional differences between visceral and subcutaneous adipocytes may be related to their anatomical location. Visceral adipose tissue and its adipose tissue-resident macrophages produce more proinflammatory cytokines, such as tumor necrosis factor alpha (TNF α) and interleukin 6 (IL6), but less adiponectin. These cytokine changes induce insulin resistance and play a major role in the pathogenesis of endothelial dysfunction and the subsequent atherosclerosis. The rate of visceral fat accumulation is also different according to the gender and ethnic background, being more prominent in white men, African American women, and Asian Indian and Japanese men and women (Hiuge-Shimizu *et al.* 2012). Such differences may explain the variation in the cardiometabolic risk between different populations. However, it is unclear as to what degree of visceral fat reduction is needed to induce favorable metabolic changes. The increasing knowledge about body fat distribution and its modifiers may lead to the development of more effective treatment strategies for subjects at a high risk for type 2 diabetes and coronary artery disease. It is interesting that visceral obesity elicits greater activation of the sympathetic nervous system (SNS) than subcutaneous obesity does (Grassi *et al.* 2004); however, the mechanism by which visceral obesity is more active in SNS activation is not clear.

The obesity-related hypertension is a multifactorial and polygenic trait (Aghamohammadzadeh & Heagerty 2012).

The multiple potential mechanisms contribute to the development of higher BP in obese humans including hyperinsulinemia, activation of the renin–angiotensin–aldosterone system, SNS stimulation, abnormal levels of certain adipokines such as leptin, and altered spectrum of cytokines acting at the vascular endothelial level (da Silva *et al.* 2009, Hall *et al.* 2010, Lambert *et al.* 2010). Moreover, the role of perivascular adipose tissue damage, defined as a disturbance in normal metabolic and vasoactive function of the adipocytes surrounding blood vessels, is also considered (Aghamohammadzadeh & Heagerty 2012). However, the exact mechanisms of the relationship between obesity and hypertension are still not fully understood. Undoubtedly, the interaction of genetic and environmental factors is also important (Kuneš & Zicha 2006). In the last years, several genetic loci and genes linked to obesity and hypertension were disclosed on different chromosomes and the list of obesity-associated loci is increasing day-by-day (Russo *et al.* 2010).

The influence of dietary factors on the development of obesity-related hypertension may be partially explained by epigenetics. These non-genetic alterations, which have an important regulatory action in modifying gene expression in response to environmental stimuli, are under the control of two major epigenetic mechanisms: methylation of cytosine residues of DNA and modification of histone proteins associated with DNA (chromatin remodeling). The epigenetic chromatin remodeling is very important because it modifies the accessibility of chromatin to transcription factors, facilitating the recognition of these factors by genes to be expressed and by genes to be silenced, either transiently or permanently (Spotswood & Turner 2002). It has been demonstrated that the disruption of balance of epigenetic networks may cause several major diseases. However, the relevance of epigenetics to obesity, hypertension, and/or metabolic syndrome is less clear (Egger *et al.* 2004, Gallou-Kabani & Junien 2005). We can speculate that obesity-related hypertension develops as a consequence of ‘errors’ in well-coordinated regulatory systems (Kuneš & Zicha 2009). The errors in the cascade of molecular, biochemical, and genetic processes, which regulate BP, glucose metabolism, food intake, etc., have finally enough potential to result in a particular disease. As these errors may not be robust and affect various parts of the complex regulatory system, their determination might be difficult (Kuneš & Zicha 2009).

This short review summarizes contemporary information on the pathophysiology of obesity-related hypertension. Special attention will be paid to the role of the SNS and the renin–angiotensin system (RAS) and the

role of ontogenetic factors in obesity-related hypertension will be discussed. We have repeatedly emphasized the importance of age in the pathogenesis of experimental hypertension (Zicha *et al.* 1986, Zicha & Kuneš 1999, Kuneš & Zicha 2006). Moreover, the hypothesis of the fetal origins of adult diseases in humans was proposed by Barker & Osmond (1988), suggesting that environmental factors, mainly nutrition, can lead to permanent metabolic and structural changes in the fetus, thus increasing the risk of many diseases in adulthood, including hypertension (Kuneš *et al.* 2012) and obesity (Taylor & Poston 2007). The knowledge of molecular mechanisms, by which early minor environmental stimuli modify the expression of genetic information, might be the desired key for the understanding of mechanisms leading to the change of phenotype in adulthood (Kuneš & Zicha 2009, Kuneš *et al.* 2012). We would also like to discuss some information about epigenetic inheritance, which should partially explain the gene–environment interaction.

Rat models of obesity and hypertension

Animal models are essential to understand the pathophysiology of human diseases; however, the ideal model, which should mimic all pathophysiological features of a particular disease, does not exist. Such a model should be genetically well defined, should be large enough for experimental techniques, economically acceptable, and would develop end-stage disease comparable to that in humans (Zicha & Kuneš 1999, Russell & Proctor 2006). Although the mouse seems to be a more appropriate tool for genetic manipulations, its small size is not good for long-term physiological measurements. Therefore, rat models are the most useful. Spontaneous mutations and selective breeding procedures in rats provide several complementary models of obesity, hyperlipidemia, insulin resistance, and type 2 diabetes, as well as cardiovascular diseases including hypertension (Russell & Proctor 2006, Fellmann *et al.* 2013). Although each animal model has some limitations and strengths, used together in a complementary fashion they are essential for the research on metabolic and cardiovascular diseases. As mentioned above, the etiology of these diseases is complex, both inherited and acquired (Kuneš & Zicha 2006, Varga *et al.* 2010).

The development of obesity and the associated metabolic complications due to increased caloric intake in rodents is a widely used approach, which is parallel to human obesity. Both rat and mouse strains susceptible to the development of obesity are fed a high-fat diet (HFD) over a period of 3–4 months (Vickers *et al.* 2011,

Fellmann *et al.* 2013). Within rat strains, Wistar and Sprague–Dawley strains are most often used. However, only some Sprague–Dawley rats fed a HFD develop obesity, dyslipidemia, and arterial hypertension (Dobrian *et al.* 2000).

Spontaneously hypertensive rats (SHRs) are considered to be a model of essential human hypertension without obesity. However, it has been demonstrated that a HFD increased body weight, serum cholesterol, and BP in SHRs and the changes in metabolic parameters were associated with cardiovascular dysfunction in these animals (Šedová *et al.* 2004, Cao *et al.* 2011). Chung *et al.* (2010) have shown that after 12 weeks on the HFD, SHRs gained more body weight, their systolic BP was further elevated, and glucose intolerance induced, but there were no significant differences in the insulin resistance index, serum lipid profile, plasma renin activity, and serum aldosterone levels. On the other hand, Knight *et al.* (2008) observed that HFD consumption for 10 weeks had no effect on systolic BP of SHRs. It seems that the discrepant results may be due to different durations of the experiment, different ages at which HFD feeding was started, and/or different compositions of the diets.

Other models, similar to obese strain of SHR (SHROB) or Zucker rats, provide interesting results in the study of obesity-related hypertension. In 1973, Koletsky isolated a new mutation in a rat line originating from a cross between Sprague–Dawley rats and SHRs. Animals of this strain were hypertensive and became highly obese, hyperlipidemic, and hyperinsulinemic. Most interestingly, obese rats developed cardiovascular disease with atherosclerosis and advanced lesions, including dissecting aortic aneurysms (Koletsky 1975). The strain, now designated as SHROB, has been recently used as a model that closely mimicks human metabolic syndrome. Several substrains of SHROB rats with diverse severity of symptoms are used (Russell & Proctor 2006, de Artiñano & Castro 2009). SHROB rats can be identified as obese at about 5 weeks of age together with hyperinsulinemia, slightly elevated blood glucose (Friedman *et al.* 1997), and insulin resistance (Velliquette *et al.* 2002). Spontaneous hypertension usually occurs at ~3 months of age and rises progressively; animals also develop cardiac hypertrophy and vascular disease (Ernsberger *et al.* 2007). Thus, one can say that obesity precedes hypertension, but it is difficult to say that obesity is a cause of hypertension in this model.

Obese Zucker rats (OZR) are the best known and most widely used animal model of genetic obesity and hypertension, which was initially described by Zucker & Zucker (1961) (Kurtz *et al.* 1989). This strain has

a spontaneous mutation of the gene for leptin receptor. Leptin is a hormone released from adipocytes and acts as a key regulator of energy homeostasis. Zucker rats develop severe obesity associated with hyperphagia, defective thermogenesis and a range of endocrinological abnormalities, and insulin resistance with mild glucose intolerance, but without a progression to diabetes (Russell & Proctor 2006, de Artiñano & Castro 2009). Moreover, it has been demonstrated that in adult OZR, renal and splanchnic sympathetic nerve activity (SNA) as well as mean arterial pressure (MAP) are elevated in comparison with age-matched lean Zucker rats (LZR) (Morgan *et al.* 1995, Huber & Schreihofner 2010). Furthermore, it has been suggested that the elevated SNA and MAP in OZR could be derived from the rostral ventrolateral medulla (Huber & Schreihofner 2011). Zucker diabetic fatty (ZDF) rats are a variant of the Zucker rats, which were developed from the original Zucker colony (Friedman *et al.* 1991). Obese male rats of this colony were found to become diabetic, with impaired insulin secretion, but with preserved sensitivity to insulin. They also developed a late increase in systolic BP (at 7 months of age), and hence they could be considered as a good model of obesity-related hypertension (Kurtz *et al.* 1989). However, it should be noted that leptin receptor mutation is extremely rare in humans (Hall *et al.* 2001). Thus, the results from the studies on Zucker rats cannot be simply applied to human obesity, which is commonly polygenic (Bell *et al.* 2005).

Peptides in cardiovascular regulation

To prevent obesity-related cardiovascular disease, it is important to clarify the mechanisms controlling food intake and to determine whether these mechanisms are also involved in BP regulation. Some peptides participating in the regulation of appetite or feeding behavior seem to have a role also in cardiovascular and sympathetic regulations. These peptides include short-term centrally released and centrally acting neuropeptide Y (NPY), corticotrophin-releasing hormone (CRH), agouti-related protein (AgRP), alpha-melanocyte-stimulating hormone (α -MSH), cocaine- and amphetamine-regulated transcript (CART) peptides, melanin-concentrating hormone (MCH), orexins, etc. Their central effects are combined with those of peripherally released and centrally acting leptin and ghrelin, which regulate energy balance in a long-term manner, and with short-term acting peptides such as cholecystokinin (CCK) (for review see Matsumura *et al.* (2003), Baltatzi *et al.* (2008) and Sartor (2013)). Peripherally released hormones play a role in short-term

cardiovascular regulation via the vagally mediated sympathoinhibitory reflex mechanism, similar to that of the arterial baroreflex (Sartor 2013).

Leptin, the product of the *ob* gene, is synthesized in the adipose tissue and serum leptin levels correlate with total fat mass. Leptin regulates energy intake and expenditure providing the information to the CNS and influencing the effects of other neuropeptides to decrease food intake and to upregulate thermogenesis and energy expenditure through the stimulation of SNA. These effects are mediated by two major pathways, positive regulation of anorexigenic α -MSH and negative regulation of NPY having an orexigenic effect combined with a reduction of thermogenesis (Kotsis *et al.* 2010). In obesity, leptin resistance and hyperleptinemia develop because of disrupted signaling in leptin receptor-containing neurons in brain areas involved in food intake regulation, namely the hypothalamic nucleus arcuatus. Leptin action in the nucleus arcuatus is also important for the control of sympathetic outflow to both brown adipose tissue and the kidney (Rahmouni & Morgan 2007). Selective resistance to the metabolic actions of leptin seems to be present in obesity, whereas its action in stimulation of sympathetic tone remains unaltered (Mark *et al.* 2004). SNS-stimulating effects of leptin are mainly demonstrated in the kidney, adrenal gland, and brown adipose tissue. Hyperleptinemia and leptin resistance thus may be the cause of chronically elevated SNS in obesity via activation of leptin receptors in hypothalamus and brainstem (Hall *et al.* 2010, Canale *et al.* 2013). In diet-induced obesity in mice, anorexigenic activity of leptin, both peripherally or centrally administered, was attenuated while renal SNA to leptin as well as increased BP were preserved, leading to hypertension (Rahmouni *et al.* 2005a).

Many studies have also examined whether the effects of leptin on metabolism, apoptosis, and hypertrophy could contribute to the obesity-related hypertension (for review see Sweeney (2010)). Moreover, in the leptin-resistant state, NPY is overexpressed and it is released from neural sites by sympathetic activation and acts as a vasoconstrictor and thus could play a role in obesity-related hypertension (Kotsis *et al.* 2010).

CCK is an anorexigenic gastrointestinal peptide with many functions related to digestion including satiety. Leptin is also released from the gastric epithelial cells of the stomach (Bado *et al.* 1998). Both hormones have an additive effect at the level of vagal afferents to regulate food intake, but CCK and leptin also have an interactive relationship in cardiovascular regulation via central mechanisms (Sartor 2013). The potential importance of

CCK and its receptor CCK1 has been demonstrated in rats lacking CCK1 receptors, which develop obesity, diabetes, cardiac disease, and hypertension (Yagi *et al.* 1997).

Ghrelin, together with leptin, is a key regulator of energy balance. It is a physiological antagonist of leptin and also acts in the hypothalamus with the opposite influence on neuropeptides such as NPY and α -MSH compared with leptin. Although ghrelin production is known to be suppressed in obesity states, high levels of ghrelin have been found in obese hypertensive patients (Zhang *et al.* 2010). The relationship among obesity, hypertension, and ghrelin needs further elucidation. The exact BP-lowering mechanisms exerted by ghrelin are unknown but probably involve central and peripheral pathways. Modulation of endothelial function may be at least partially responsible for the antihypertensive actions of ghrelin. BP-lowering effect of i.v. ghrelin administration in rats occurred together with a decrease in SNA and was not caused by the direct ghrelin action on blood vessels (Callaghan *et al.* 2012). Moreover, a novel vascular receptor different from ghrelin receptor GHS-R1a was proposed to be involved in lowering of BP after the activation with growth hormone secretagogue analogs or ghrelin agonists in rats (Callaghan *et al.* 2014). In addition, it has been demonstrated that the calcium-activated potassium channel may play a key role in the BP-lowering effect of ghrelin especially in situations of endothelial dysfunction (Shinde *et al.* 2005).

The role of SNS

Increased SNA is a characteristic feature of many animal models of obesity (Kassab *et al.* 1995, Rahmouni *et al.* 2005a, Prior *et al.* 2010). High SNA has also been demonstrated in human obesity (Grassi *et al.* 1995, Vaz *et al.* 1997, Wofford *et al.* 2001) in which acute systemic ganglionic blockade lowers BP and peripheral resistance more in normotensive obese subjects than in lean subjects (Shibao *et al.* 2007). There is a considerable heterogeneity of regional SNA in obese subjects (Vaz *et al.* 1997; Fig. 1). Increased SNA detected in various vascular beds of obese subjects need not have the same importance for obesity-related hypertension. Thus, substantially enhanced muscle SNA in normotensive obese subjects does not cause the increase in forearm vascular resistance because vasodilator response of α -adrenergic blockade was similar in obese and lean subjects (Agapitov *et al.* 2008). On the other hand, moderately increased renal SNA seems to be of greater importance for the development of obesity-related hypertension (Hall *et al.* 2010). The enhancement of renal

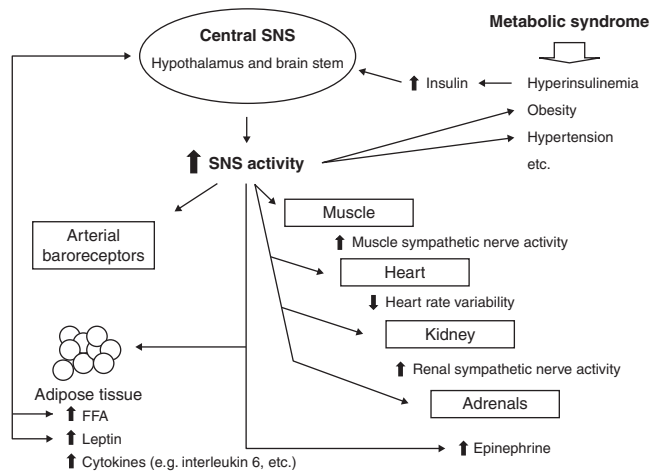


Figure 1
Particular metabolic and other effects of SNS activation.

SNA due to the impairment of baroreflex function precedes BP rise in rabbits with diet-induced obesity (Armitage *et al.* 2012). Moreover, renal denervation attenuated sodium retention and prevented BP rise in dogs with diet-induced obesity (Kassab *et al.* 1995). Similarly, chronic α - and β -adrenergic blockade lowered BP more in obese subjects than in lean hypertensive subjects (Wofford *et al.* 2001). The importance of renal sympathetic effects on obesity suggests a possible role of a recently described pathway, which is based upon norepinephrine stimulation of β_2 -adrenergic receptors leading through suppression of serine–threonine protein kinase WNK4 to the activation of Na–Cl cotransporter in the distal tubule. This β_2 –WNK4–NCC pathway is responsible for sodium retention and BP elevation in salt hypertension (Mu *et al.* 2011).

Increased levels of circulating leptin and insulin as well as decreased levels of ghrelin and adiponectin were proposed to contribute to the enhancement of SNA in obesity, but impaired baroreflex sensitivity and brain RAS must also be considered (da Silva *et al.* 2014). One of the most important mechanisms for the induction of sympathoexcitation is the action of leptin on hypothalamic pro-opiomelanocortin (POMC) neurons (Carlyle *et al.* 2002, da Silva *et al.* 2004, Tallam *et al.* 2006, do Carmo *et al.* 2014). Brain RAS is a necessary prerequisite for leptin-induced sympathetic activation (Hilzendegeger *et al.* 2012). Leptin stimulation of its receptors in POMC neurons (located in the nucleus arcuatus and/or dorsal and ventral medial hypothalamic nuclei) causes the activation of melanocortin receptor 4 (MC4R), which is mediated by α -MSH released from POMC neurons. MC4R antagonism

lowers BP of SHRs to the same extent as α -adrenergic blockade (da Silva *et al.* 2008). Moreover, normotensive LZRs respond to MC4R antagonism by a smaller BP decrease than hypertensive OZRs (do Carmo *et al.* 2012).

In normal animals, central leptin action is associated with decreased appetite, increased energy expenditure, body weight reduction, and sympathetic activation, whereas obese animals are characterized by selective leptin resistance that attenuates metabolic but not sympathetic response to leptin (Mark 2013). The concept of selective leptin resistance (Mark *et al.* 1999, 2002, Correia *et al.* 2002, Rahmouni *et al.* 2002, 2005a) is based upon the fact that yellow agouti obese mice and diet-induced obese mice were resistant to food intake and body weight effects of systemic leptin administration while leptin-induced renal sympathetic activation was preserved. It means that increased leptin levels in obese animals or subjects stimulate renal SNA but they do not exert inhibitory effects on appetite, thermogenesis, and body weight. This is partially analogous to insulin resistance, which is also selective because high insulin levels elicited by hyperglycemia do not increase glucose uptake in tissues although they stimulate SNA (Landsberg 1986). Comparison of the two selective resistances, which share a common pathway of SNS activation, is shown in Fig. 2. Insulin resistance was also suggested to participate in the pathogenetic mechanisms of hypertension (Rahmouni *et al.* 2003), but there is considerable evidence against its major role in obesity (Hall *et al.* 1990, Rocchini *et al.* 2004).

As far as selective leptin resistance is concerned, there is an idea (Kalil & Haynes 2012) that increased thermogenic SNA and decreased food intake are caused by leptin action

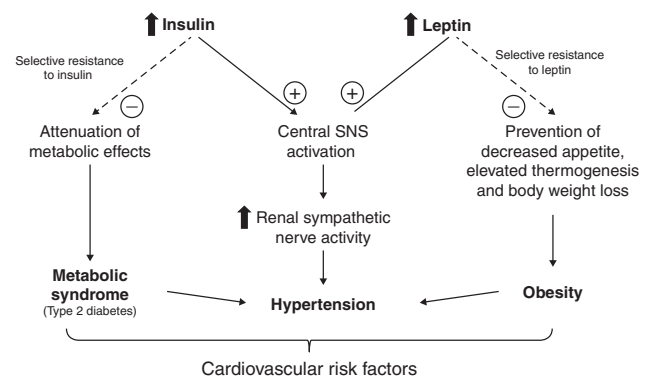


Figure 2
Selective resistance to insulin (metabolic syndrome) or leptin (obesity) – the relation to sympathetic nervous system (SNS) hyperactivity and high blood pressure.

in the nucleus arcuatus, whereas the enhanced renal SNA is due to leptin stimulation of dorsal and ventral medial hypothalamic nuclei. Another idea is that the stimulation of hypothalamic leptin receptors activates several intracellular signaling pathways including STAT3, PI3K, and MAPK (Kalil & Haynes 2012), but only the PI3K signaling pathway is capable of activating renal SNA (Mark 2013). A further important feature of selective leptin resistance is that baroreflex activation attenuates leptin-induced renal SNA, but leptin-induced sympathetic output to thermogenic tissues is not inhibited by baroreflex, thus indicating the independence of renal and thermogenic SNAs (Hausberg *et al.* 2002, Kalil & Haynes 2012). The importance of baroreflex control of SNA is underlined by the effects of chronic baroreflex activation in dogs with diet-induced obesity, which caused major renal and systemic sympathoinhibition leading to BP reduction, decrease in plasma norepinephrine and renin levels as well as to lower glomerular filtration but increased fractional sodium excretion. BP changes induced by chronic baroreflex activation were comparable to those induced by renal denervation in the dogs fed the same HFD (Lohmeier *et al.* 2012).

The analysis of heart rate variability (HRV) in obese subjects indicates that HRV is inversely related to BMI (Laederach-Hofmann *et al.* 2000, Tentolouris *et al.* 2003). In most studies, the low-frequency/high-frequency (LF/HF) ratio (an index of the sympathovagal balance) was found to be increased in obese subjects in the fasting state, suggesting a predominance of SNS activity (Tentolouris *et al.* 2003). Furthermore, parasympathetic activity was reduced in obese subjects compared with lean subjects (Laederach-Hofmann *et al.* 2000). The diminished HRV in obese individuals might indicate either reduced receptor responsiveness or postreceptor alterations involving the cardiac sinus node. However, the power of the low-frequency component of the HRV seems to provide an index of the baroreflex modulation of SNS activity. Hence, a reduced power of the low-frequency component of the HRV could reflect diminished baroreflex sensitivity to the changes in BP (Piccirillo *et al.* 1998). Such a diminished responsiveness has been confirmed by other studies using the measurements of postganglionic muscle SNA in response to the changes in MAP elicited by stepwise i.v. nitroprusside or phenylephrine infusions (Grassi *et al.* 1995). They have demonstrated that baseline BP and heart rate as well as plasma norepinephrine levels were similar in obese and control subjects. However, muscle SNA was more than twice higher in obese patients. Furthermore, cardiovagal baroreflex gain was found to be lower in

subjects with higher abdominal visceral fat as well as in those with higher total body fat (Beske *et al.* 2002).

Sympathetic activity is altered by food intake; it consistently decreases after energy restriction in both animals and humans and it is activated by overfeeding (Julius *et al.* 2000). It is well known that fasting lowers sympathetic activity in rats and that the ingestion of sucrose solutions increases sympathetic activity in mice (Young & Landsberg 1980). There is a highly significant inverse relationship between sympathetic activity and spontaneous food intake (Sakaguchi *et al.* 1988). The inverse relationship between SNA and food intake is of considerable interest, because it suggests a potential feedback loop between sympathetic activity and food intake (Bray 2000). The reciprocal relationship between food intake and sympathetic activity is robust, suggesting that β -adrenergic receptors in the periphery and brain may be involved in the control of food intake in humans. Thus, the inhibition of feeding by activating the SNS might be an important satiety system, which helps to regulate body fat stores and the obesity. However, this is rather difficult for patients who are taking β -blockers in the treatment of hypertension. An increase in body weight has been shown to occur during both short-term (Townsend & Klein 1997) and long-lasting (Lithell *et al.* 1992) therapies with β -blockers. The increase in body weight caused by this therapy could be a result of their negative effects on thermogenesis and/or decreased physical activity of treated patients. Propranolol administration to hypertensive subjects significantly lowers heat production rate in skeletal muscles by $\sim 25\%$. Moreover, body weight gain after β -blocker therapy might be also due to a decreased physical activity.

Renin-angiotensin system

The RAS is generally accepted as an important regulator of water and electrolyte balance and thus BP. Apart from the systemic RAS, locally acting RAS has been identified in different organs, including brain, pancreas, kidney, heart, and also adipose tissue (Paul *et al.* 2006). Locally acting RAS contains all components of RAS, including angiotensinogen (Agt), renin, and angiotensin-converting enzyme (ACE) together with AT₁ and AT₂ receptors (Cassis *et al.* 2008) to produce the main effector of the system, angiotensin II (Ang II). While Agt is produced mainly in the liver of lean individuals, adipose tissue is another important source of Agt in obese individuals (Yasue *et al.* 2010). The specific feature of adipose tissue RAS is its ability to produce Ang II not only via the renin and ACE

pathway but also through cathepsins and chymase (Karlsson *et al.* 1998). The fact that particular components of RAS are expressed in multiple tissues, including adipose tissue, suggests that this system may be associated with hypertension and obesity.

Formerly, adipose tissue has been considered only as a store for excess energy. At present, it is well recognized that adipocytes exert various physiological functions, including BP control (through Agt production) (Thatcher *et al.* 2009, Kalupahana & Moustaid-Moussa 2012). Moreover, they synthesize various hormones with homeostatic function (adipokines). The localization of *Agt* mRNA expression in adipose tissue was disclosed by Campbell & Habener (1987) and Cassis *et al.* (1988). They demonstrated it in perivascular adipose tissue surrounding the rat aorta as well as in periaortic and periaortic rat brown adipose tissue respectively. The importance of adipose Agt has been substantiated by Massiera *et al.* (2001) in transgenic mice overexpressing Agt in adipocytes on a WT or *Agt*-deficient background. They found detectable circulating Agt concentration in *Agt*-deficient mice with Agt expressed only in adipocytes and these mice were normotensive. By contrast, in WT mice, the transgenic overexpression of adipocyte Agt not only increased circulating Agt concentration but also increased BP. By contrast, mice with deleted adipocyte Agt had a lower BP than their WT counterparts (Yiannikouris *et al.* 2012a). Not surprisingly, *Agt* mRNA expression levels were higher in visceral adipose tissue of Sprague–Dawley rats with diet-induced obesity and hypertension (Boustany *et al.* 2004). In addition, losartan treatment (AT₁ receptor blocker) was more effective in obesity-prone Sprague–Dawley rats than in obesity-resistant Sprague–Dawley rats, in which hypertension was induced by a HFD (Boustany *et al.* 2005). In humans, obesity is associated with increased plasma and adipose tissue Agt, renin, ACE, and Ang II, showing both systemic and adipose tissue overactivity of RAS. Importantly, body weight loss in humans has led to the lowering of the RAS overactivity (Engeli *et al.* 2005).

Recently, Yiannikouris *et al.* (2012b) have evaluated the importance of adipose tissue RAS in the development of obesity-related hypertension using a low-fat diet and a HFD. They found that a HFD induced increase in BP only in WT mice, while there was no increase in BP in mice lacking the *Agt* gene only in adipocytes. Interestingly, mice of both types gained weight similarly and had similar amounts of fat mass on a HFD. The most interesting finding of this study was similar plasma Agt protein levels in WT and knock-out mice, which is in contrast with the previously accepted hypothesis that the increased adipose

tissue *Agt* gene expression is responsible for high plasma Agt levels and the activation of systemic RAS in obesity. However, plasma Ang II level was increased in WT mice fed a HFD but not in knock-out mice. Thus, whether this could be a link explaining the effect of local adipose RAS on the synthesis of circulating Ang II remains yet to be determined.

Obesity also leads to a shift of adipose tissue immune cells such as macrophages to pro-inflammatory status, causing hypertrophy of adipocytes and changes in the proportion of immune cell populations. A HFD induced adipose tissue inflammation and activation of adipocyte RAS, suggesting a role for Ang II in this process (Rahmouni *et al.* 2005b). In line with this finding there is the activation of pro-inflammatory cytokines (TNF α , IL6, and IL1) by Ang II in adipocytes as demonstrated by *in vitro* studies.

Early-life origins of disease

The hypothesis on the fetal origins of adult diseases in humans was proposed by Barker & Osmond (1988), who suggested that environmental factors, mainly nutrition, can lead to permanent metabolic and structural changes in the fetus and thus can increase the risk of many diseases in adulthood. Recently, we have summarized the importance of critical developmental periods in the pathogenesis of hypertension (Kuneš *et al.* 2012). We believe that some basic characteristics of hypertension development can be applied for the development of other significant diseases. It is also very important to take into consideration that developmental changes need not be detected immediately after the intervention. A certain delay is always present, so that one can speak about the 'late consequences of early alterations'. There is no doubt that the critical developmental periods are much better recognized and characterized in experimental animals than in humans (Zicha & Kuneš 1999, Kuneš *et al.* 2012). However, as mentioned earlier, this theory can also be applied in humans. In 1986, David Barker and his colleagues postulated that the geographical distribution of mortality rates from stroke and cardiovascular diseases in 1968–1978 was closely related to the neonatal mortality in 1921–1925, suggesting that poor health and physique of mothers were the important determinants of the risk of stroke in their babies (Barker & Osmond 1986). Later on, they reported that BP in adulthood was related not only to the birth weight but also inversely to the placental weight (Barker *et al.* 1990), leading to the formulation of the 'early or fetal

origin' hypothesis. Thus, the intrauterine period might be a major critical period for human diseases.

The detailed review of 48 papers clearly documented the relationship between early growth and the later occurrence of insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, and cardiovascular diseases in both men and women in distinct populations in the UK, Asia, Europe, Africa, and the USA (Newsome *et al.* 2003). The combination of low birth weight followed by obesity in later life appears to carry the highest risk of insulin resistance.

It has been demonstrated that fetal overexposure to maternal glucocorticoids in both humans and animals triggers programming events *in utero* (Langley-Evans 1996, 2006, Nyirenda & Seckl 1998). Glucocorticoids are powerful modulators of gene expression and experimental studies have demonstrated that they accelerate fetal organ maturation. This has been proposed as a key step in nutritional programming. The administration of synthetic glucocorticoids, which are poor substrates of 11 β -hydroxysteroid dehydrogenase type 2, programs hypertension and renal defects in animals (Benediktsson *et al.* 1993, Dodic *et al.* 2002). Feeding of a low-protein diet to rats during pregnancy reduces both the activity and mRNA expression of placental 11 β -hydroxysteroid dehydrogenase type 2 (Langley-Evans *et al.* 1996, Bertram *et al.* 2001). Moreover, the blockade of maternal glucocorticoid synthesis through pharmacological adrenalectomy prevents the programming of hypertension in the offspring of rats fed a low-protein diet, demonstrating the glucocorticoid dependence of the nutritional effect (Langley-Evans *et al.* 1996, Langley-Evans 1997, McMullen & Langley-Evans 2005). This is also true for humans in whom exogenous glucocorticoids retard fetal and placental growth and result in lower birth weight (Hofmann *et al.* 2001). This is corroborated by the fact that there are strong correlations among birth weight, plasma cortisol concentrations, and the development of hypertension and type 2 diabetes (Phillips *et al.* 2000). As perinatal exposure to glucocorticoids increases the activity of hypothalamic–pituitary–adrenal axis (Holmes *et al.* 2003, Bouret 2009), it has been proposed that the programming of this axis *in utero* is linked to behavioral modifications and neurological responses, as well as endocrine and cardiovascular functions.

Accumulating body of evidence demonstrated that leptin production from the placenta and fetal adipose tissue can regulate fetal growth and development (Stocker *et al.* 2005). Besides the regulation of energy balance and neuroendocrine functions in mature animals, this is

another function of leptin. Administration of leptin during pregnancy and lactation to protein-restricted dams produced offspring that had increased metabolic rate and thus they were not obese when fed a HFD in adulthood (Stocker *et al.* 2005). This is probably due to the fact that neonatal leptin is an important trophic factor for the development of hypothalamic circuits (Bouret 2009). The existence of the critical periods for the developmental effects of leptin during key periods of hypothalamic development may induce long-lasting effects on the metabolism in adults.

Epigenetic mechanisms

Despite the enormous progress in genetic and genomic studies, including extensive analysis of the human genome, only up to 10% of discovered gene functions are known and many more remain yet to be discovered. It is evident that genetics alone cannot explain the occurrence of phenotypic heterogeneity of cardiovascular diseases including hypertension and obesity. Probably, the interaction of organism with environmental factors is dependent on several other features such as epigenetics. Epigenetics is not based upon changes in nucleotide sequence of DNA, but it is associated with DNA methylation, histone modifications, and chromatin remodeling. More than 100 modifications of histones including acetylation, methylation, phosphorylation, etc., have been described (Kouzarides 2007). Although the function of most of these 'marks' remains obscure, there is a possibility that they determine which genes are transcribed in which cells under specific circumstances. It has been shown that unusually dense collections of CpG dinucleotides known as CpG islands exist throughout the genome (Eckhardt *et al.* 2006). These islands are localized in promoter regions of particular genes and they are not methylated during transcription. Additionally, the chromatin proteins associated with DNA may be activated or silenced. This explains why the differentiated cells in a multicellular organism express only those genes that are necessary for their own activity.

There is no doubt that gene–environment interactions play a significant role in the etiology of obesity-related hypertension and other diseases. One would expect that the environmental impact (diet, lifestyle, working conditions, smoking, various infectious agents, etc.) on genetic information is exerted via DNA damage, but epigenetic inheritance seems to be more responsible (Kuneš & Zicha 2006). Several recent studies have demonstrated how environmental factors can modify

epigenetic processes, thereby affecting epigenetic marks and downstream patterns of gene expression in specific cells and cell lineages (Roche *et al.* 2005, Gluckman *et al.* 2007, Waterland & Michels 2007, Feinberg 2008). Epigenetic changes not only occur in the course of individual organism's lifetime, but also may be inherited from one generation to the next. It seems that environmental conditions influencing the organism during its lifetime may activate specific silent alleles or suppress others. The epigenome is a connection between environmental exposure and gene expression, thus influencing cell/tissue function. This may be especially important for the early life (*in utero*) exposure. In the earliest stages of life, the genome undergoes radical changes in epigenetic marks, which are characterized by waves of demethylation of DNA followed by remethylation (Reik *et al.* 2001). These imprinting patterns, if not erased after fertilization, may become stable and persist to the next generations of experimental animals (Zambrano *et al.* 2005, Pinheiro *et al.* 2008, Torrens *et al.* 2008) and even of humans (Veenendaal *et al.* 2013). This can be reversed by the changes in lifestyle (Gallou-Kabani & Junien 2005). For example, it was observed that protein restriction during pregnancy of rats can result in hypomethylation of peroxisome proliferator-activated receptor alpha (Lillicrop *et al.* 2008), hepatic glucocorticoid receptor promoters (Lillicrop *et al.* 2005), and angiotensin AT_{1b} receptor in the offspring (Bogdarina *et al.* 2007). Intra-uterine exposure to a low-protein diet may increase the risk of hypertension also by the increased corticosteroid levels. The transgenerational effects could be triggered through environmental factors such as food preferences, special dietetic factors, and physical activity. For example, in the agouti mouse model, folate supplementation of the maternal diet at conception augments DNA methylation of the agouti gene and increases longevity of the offspring (Cooney *et al.* 2002).

Recently, it has been shown that complex diseases such as obesity or hypertension may be related to highly interconnected gene networks and core network modules that are deregulated by susceptibility loci (Emilsson *et al.* 2008, Mehler 2008). Moreover, not only gene networks but also environmental factors and epigenome, more complex networks can collaborate in clinical manifestations of specific disease states (Fig. 3). On the basis of animal models of disease as well as of human clinical trials, there are currently three classes of epigenetic therapies i) DNA methylation inhibitors, ii) histone deacetylase (HDAC) inhibitors, and iii) RNA-based approaches (Ptak & Petronis 2008).

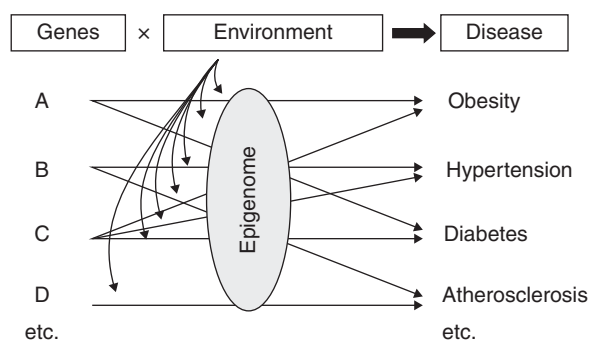


Figure 3

The interaction of genes, environment, and epigenome in the etiology of polygenic diseases.

The study of epigenetic and developmental processes could shed new light on serious health problems. For example, protein restriction in pregnant rats reduces methylation of the promoter region of the gene that codes for glucocorticoid receptor in offspring liver cells (Lillicrop *et al.* 2007, Erhuma *et al.* 2009). This leads to the amplification of the liver metabolic response to stress hormones. Moreover, it has been demonstrated that pups of rat mothers on a low-protein diet overexpress the AT_{1b} receptor mRNA and protein in the adrenal gland, suggesting its contribution to the elevated BP observed in these animals (Bogdarina *et al.* 2007). The expression of AT_{1a} receptor was normal. However, such results cannot be simply transferred into human pathology because human genome contains only a single AT₁ receptor gene, which is widely expressed in a pattern similar to that of AT_{1a} receptor in rodents (Inagami 1995). Besides the role of the prenatal environment, including nutrition, the effects of prenatal stress and social environmental exposures can be important factors (Darnaudéry & Maccari 2008, Kuzawa & Sweet 2009). Therefore, the study of epigenetic contributions to obesity-related hypertension and other cardiovascular diseases should be very important for the understanding of other regulatory mechanisms and for the development of new therapeutic strategies as mentioned in several recent reviews (Wong *et al.* 2005, Turunen *et al.* 2009, Ordovás & Smith 2010, Lillicrop & Burdge 2012).

Conclusions

Obesity-related hypertension is an important medical problem. According to the epidemiological studies, we can talk about the pandemic of obesity and thus partially also about the epidemic of hypertension. Obesity-related hypertension is a chronic, slowly developing disease the

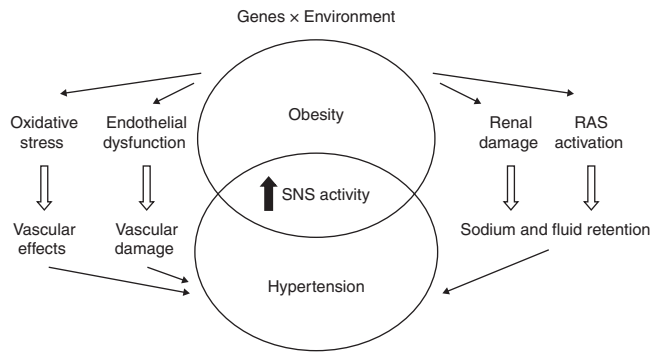


Figure 4
Relation between obesity and hypertension as well as particular mechanisms by which obesity may cause hypertension.

pathology of which is complex, and multiple potential mechanisms could play a role in the relation between obesity and hypertension (Fig. 4). Despite the fact that many details about the development and maintenance of obesity-related hypertension have been identified, the primary impulse to start the pathological process is still not known, and neither is it known whether obesity causes hypertension or *vice versa*. Nevertheless, it has been demonstrated (Messerli *et al.* 1981) that obesity *per se* raises BP by only a few millimeters of mercury, while 50% of individuals with hypertensive obesity have a much larger rise in BP (Korner 2007).

Gene–environment interactions are gaining more and more attention in the etiology of human diseases. There is an increasing belief that epigenetic variants and inheritance could provide the missing piece of a puzzle for the understanding of these very complicated relationships in many diseases, which have usually the complex phenotypes, e.g. obesity-related hypertension. Studies on genetic association have had a mixed success in the detection of important genes and/or environmental influences that are notoriously difficult to identify. Thus, epigenetic changes and regulation become increasingly important. The research community is increasingly aware of the role that chromatin plays in gene regulation, transcription, and disease development.

However, once the obesity-related hypertension has developed, the complete normalization of BP is difficult, if not impossible. The main concern for the future should be therefore the prevention of obesity and/or hypertension development as well as the personalized medicine. There is no doubt that the young organism is highly sensitive to various risk factors and it may also be more sensitive to various pharmacological interventions than the adult one.

Therefore, the early diagnosis of obesity, hypertension, and other diseases together with the change in lifestyle can lead to early intervention and thereby can improve the health of the whole population. However, the question whether obesity prevention will reduce hypertension and *vice versa* remains yet to be clarified. The proper understanding of the important mechanisms in obesity-related hypertension and other complex diseases in experimental animals together with the precise determination of the critical developmental periods for the onset of these diseases might be the first step toward the development of new therapies in human medicine.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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