

REVIEW

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Autonomic nervous system activity changes in patients with hypertension and overweight: role and therapeutic implications

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Abstract

The incidence and prevalence of hypertension is increasing worldwide, with approximately 1.13 billion of people currently affected by the disease, often in association with other diseases such as diabetes mellitus, chronic kidney disease, dyslipidemia/hypercholesterolemia, and obesity. The autonomic nervous system has been implicated in the pathophysiology of hypertension, and treatments targeting the sympathetic nervous system (SNS), a key component of the autonomic nervous system, have been developed; however, current recommendations provide little guidance on their use. This review discusses the etiology of hypertension, and more specifically the role of the SNS in the pathophysiology of hypertension and its associated disorders. In addition, the effects of current antihypertensive management strategies, including pharmacotherapies, on the SNS are examined, with a focus on imidazoline receptor agonists.

Keywords: Autonomic nervous system, Hypertension, Obesity, Type 2 diabetes, Selective imidazoline receptor agonists

Introduction

Hypertension is one of the leading causes of premature death worldwide with 1.13 billion people having hypertension. It is associated with an increased risk of cardiovascular diseases (CVD; e.g., stroke, angina, myocardial infarction, heart failure, peripheral artery disease, and abdominal aortic aneurysm) as well as end-stage renal disease [1, 2]. Hypertension often co-occurs with other CVD risk factors such as diabetes mellitus, dyslipidemia/hypercholesterolemia, obesity and chronic kidney disease [1, 3, 4]. Despite several actions set up to improve diagnosis, management and awareness about hypertension, the incidence and prevalence are still increasing [5,

6]. The prevalence of hypertension is higher in low- and middle-income countries [5] and increases with age [1].

The autonomic nervous system has been implicated in the pathophysiology of hypertension [7, 8] and treatments targeting the sympathetic nervous system (SNS) have been developed [9, 10] although largely forgotten or ruled out in international recommendations [1, 2]. The aim of this review, therefore, is to examine the pathophysiology of hypertension, in particular the role of the autonomic nervous system (ANS) and medications that target the SNS to help control hypertension. A search of PubMed was conducted using search terms such as “hypertension”, “blood pressure”, “sympathetic nervous system” and “SNS”, with no restrictions on date of publication. Supplemental, focussed ad-hoc searching was conducted where necessary.

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Hypertension

According to the ESC/ESH guidelines, hypertension is defined as office systemic blood pressure values ≥ 140 mmHg and/or diastolic blood pressure values ≥ 90 mmHg [2].

The aetiology of hypertension is currently still poorly known, although several risk factors have been identified for its development such as overweight, diet (e.g., sodium intake), physical activity, and alcohol consumption [11, 12]. Its pathogenesis is multifactorial and highly complex, involving multiple organ systems and numerous independent and interdependent pathways [13]. Known systems involved in blood pressure control include cardiovascular, renal, neural, and endocrine systems, as well as local tissues, with the kidneys playing a central role [13]. In addition, genetic factors, and activation of neurohormonal systems are involved in the pathogenesis of hypertension. The neurohormonal system is responsible for maintenance of cardiovascular homeostasis, with the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) being two key components [14]. RAAS is involved in the maintenance of arterial blood pressure, plasma sodium concentration and extracellular volume, and needed for the function of the heart and kidneys. RAAS dysfunction can lead to chronic diseases development as hypertension or heart failure [15, 16].

While animal studies have demonstrated extensive and reciprocal interactions between SNS and RAAS important to cardiovascular regulation and the development of hypertension, supportive evidence in humans is currently lacking [17, 18].

The sympathetic nervous system

Physiological role of the sympathetic nervous system

Maintenance of cardiovascular homeostasis requires continual redirection of blood flow to ensure adequate blood supply to active tissues. Under normal functioning, the autonomic nervous system, comprising the sympathetic, parasympathetic and enteric nervous systems, makes unconscious adjustments in regional blood flow and cardiac output, and coordinates with the central respiratory network in order to respond to varying metabolic and thermoregulatory demands [19]. The SNS is activated when baroreceptors, specialised stretch receptors located within thin areas of blood vessels and heart chambers, sense changes in pressure [20]. When arterial pressure drops, the SNS is immediately activated resulting in increased cardiac output and vasoconstriction of peripheral vessels (Fig. 1) [20]. Subsequent constriction of renal afferent arterioles results in activation of the renin–angiotensin–aldosterone system and secretion of renin [14].

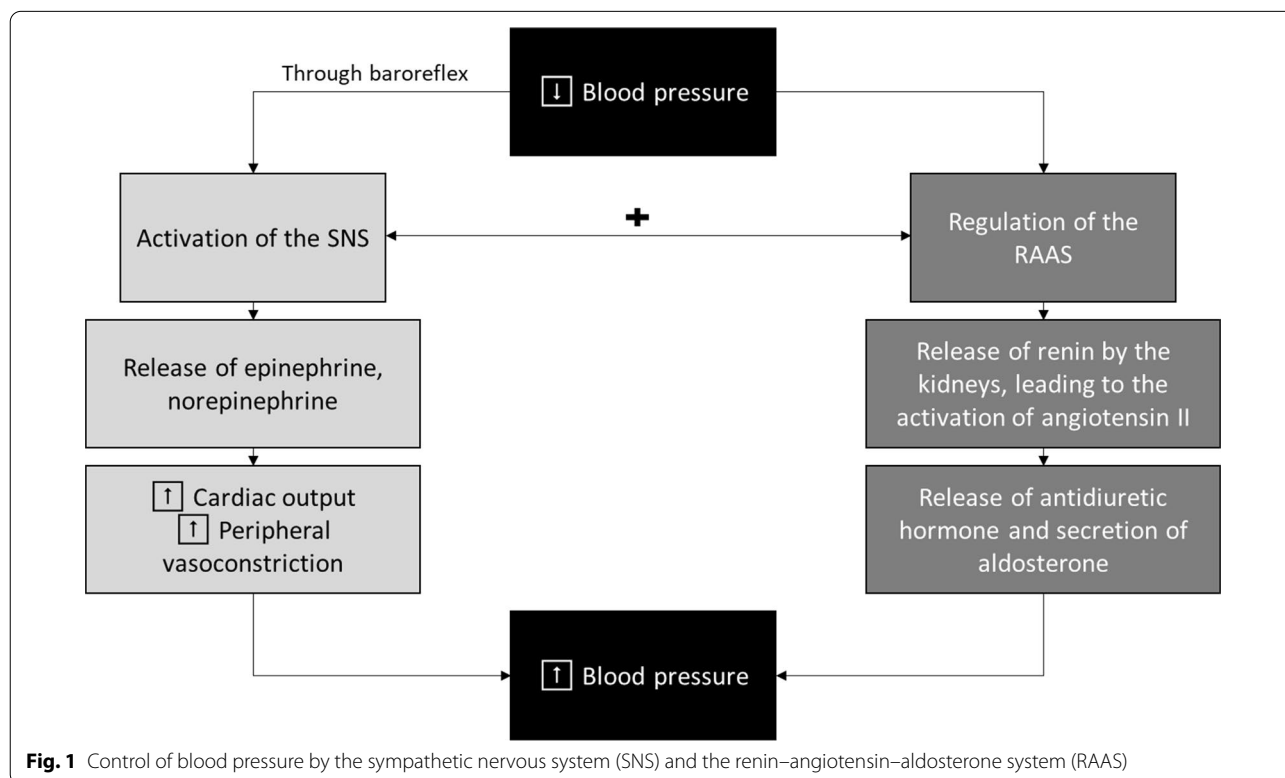


Fig. 1 Control of blood pressure by the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS)

The SNS plays an important role in the regulation of liver metabolic processes, with the sympathetic and parasympathetic systems working in tandem to respectively stimulate and suppress hepatic gluconeogenesis, and insulin stimulating glycolysis and lipogenesis, and suppressing gluconeogenesis [21]. Overall, the SNS enhances the production of glucose by the liver and mobilises metabolic fuels for use by the tissues [21]. In the pancreas, Langerhans islets are innervated by autonomic nervous system fibres resulting in modulation of insulin secretion with parasympathetic nerves stimulating insulin secretion and sympathetic nerves having the opposite effect [22, 23]. Enhanced lipolysis in adipose tissue by the SNS is part of a control mechanism designed to break down fats [24].

SNS overdrive in hypertension

The consequences of sympathetic overdrive leading to hypertension are numerous and include cardiovascular, renal and metabolic effects (Fig. 2) [25–27]. A state of sympathetic activation is associated with increased heart rate, and appears to promote cardiac and vascular alterations [25, 28], contributing to the development of major complications of hypertension such as arrhythmia, left

ventricular hypertrophy and increased arterial stiffening [25–29]. The SNS also appears to affect haemostasis, with acute activation of the SNS resulting in hypercoagulability due to increased platelet aggregability [29, 30].

Sympathetic activity is increased in hypertension and heart failure, and is responsible for initiation and development of the diseases [7, 8, 31]. While specific causes of this increase are mostly unknown, genetic influences, behavioural and lifestyle factors appear to be involved [7, 8]. Increased SNS activity is believed to contribute to the pathophysiology of heart failure through multiple mechanisms, including desensitization of cardiac β -adrenergic receptors, adverse effects on excitation–contraction coupling, and fibrosis [16, 32].

The effects of the SNS activation are mediated by adrenergic neurotransmitters (norepinephrine, epinephrine and dopamine) having vasoconstriction properties [18]. It has been shown that the norepinephrine spillover is increased in patients with high blood pressure, and this increase is mainly seen in the heart and the kidneys, both tightly involved in blood pressure control [18]. The release of these adrenergic neurotransmitters induces action on cardiovascular and metabolic systems by targeting organs involved in homeostasis control as

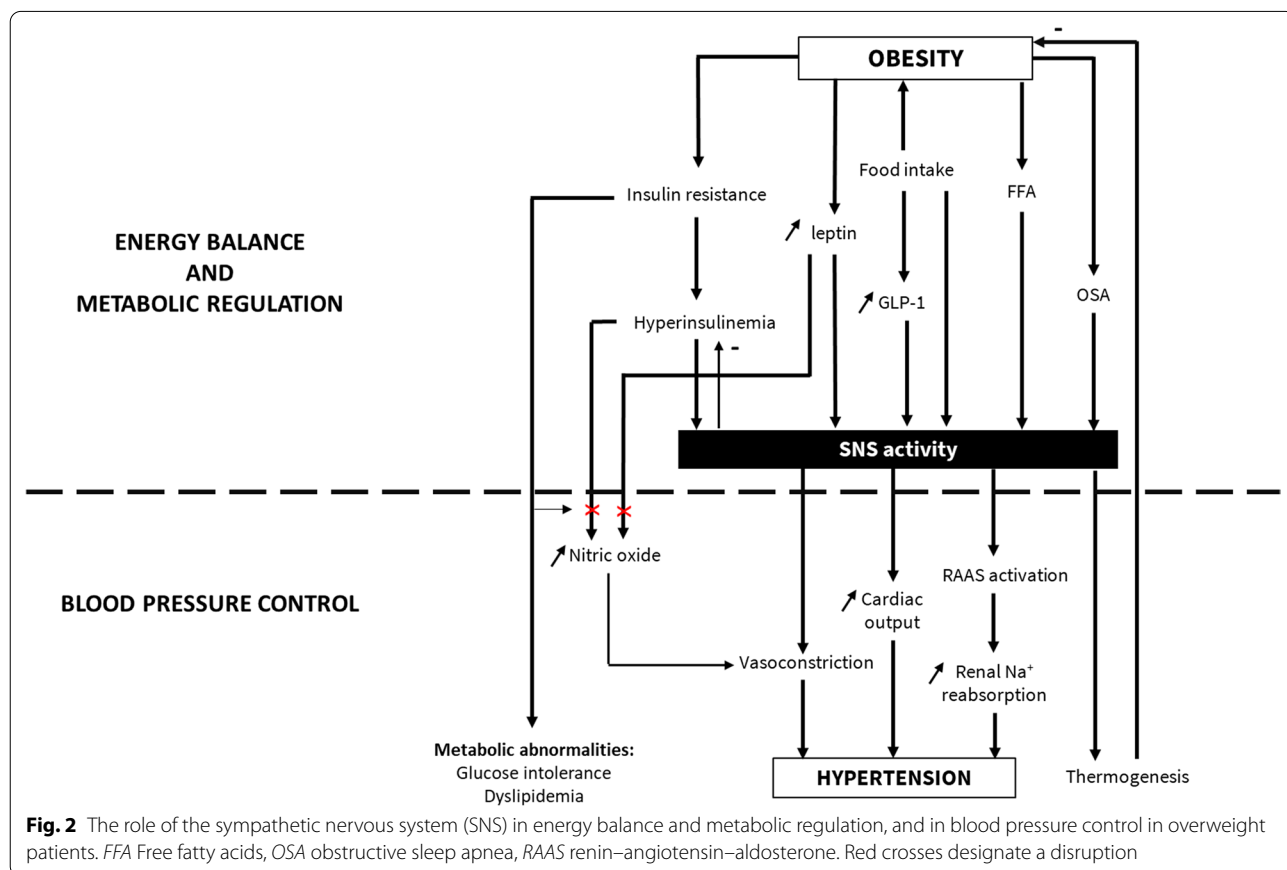


Fig. 2 The role of the sympathetic nervous system (SNS) in energy balance and metabolic regulation, and in blood pressure control in overweight patients. FFA Free fatty acids, OSA obstructive sleep apnea, RAAS renin–angiotensin–aldosterone. Red crosses designate a disruption

the heart, kidneys, veins, and arterioles, and leading to renin release, sodium retention, increase in heart rate, arrhythmias, and left ventricular hypertrophy. Thus, these targets of the SNS contribute to increase blood pressure. Regarding the metabolic effects, the adrenergic neurotransmitters are responsible for action on different organs and tissues: on fat cell to increase lipolysis resulting in an increase in fatty acid release, on the liver to increase gluconeogenesis, on pancreatic β -cells to decrease insulin secretion. Conversely, free fatty acids may enhance sympathetic activity [33]. If the sympathetic activity is raised chronically, it may lead to development of insulin resistance and hypertension, increasing the risk of cardiovascular diseases. The role of therapeutic inhibition of sympathetic overdrive in the prevention of the metabolic disorders and the associated adverse outcomes requires adequate testing in properly sized randomised controlled trials [8, 21, 24, 31, 34–38].

In contrast to increased sympathetic activity, parasympathetic activity is decreased in patients with hypertension, suggesting a sympathetic/parasympathetic imbalance [39–41].

A higher prevalence of hypertension is found in diabetic patients with a defective parasympathetic control. Moreover, there is an association between this defect and hypertension profile and vascular complications [42].

As well as being involved in hypertension, abnormal activation of the SNS has been implicated in metabolic syndrome, known risk factors for hypertension [4, 43].

Obesity, obesity-related hypertension and SNS overdrive

Hypertension is common in obese individuals. It is estimated that about 75% of hypertension incidence is directly linked to the presence of obesity (defined by a body mass index ≥ 30 kg/m²).

A dysfunction of the SNS activity leads to weight gain. Indeed the SNS plays a critical role in controlling energy expenditure in response to certain physiological stimuli (e.g., changing energy states, food intake, carbohydrate consumption, hyperinsulinemia, and exposure to cold) via regulation of the resting metabolic rate and initiation of thermogenesis by action on the brown adipose tissue [43, 44].

However, obesity is associated with SNS overdrive which is considered as a compensatory mechanism for the increase in energy expenditure, thus allowing to restore the energetic balance [45]. In particular SNS activity was shown to correlate with visceral adiposity [46]. Such SNS overdrive may contribute to metabolic disorders as insulin resistance with subsequent hyperinsulinemia, impaired glucose metabolism, diabetes, dyslipidemia [47, 48]. Obesity is also often linked to resistant hypertension, characterized by an incapacity to control

blood pressure despite the prescription of at least three anti-hypertensives agents, including a diuretic [48].

However, some data suggest that sympathetic response to various stimuli may be blunted in obese patients compared to lean individuals. For instance, sympathetic activity was reported in obese patients to be less stimulated after a meal rich in carbohydrates or oral glucose intake despite a higher insulin response [49–51], and they exhibit a lower hemodynamic response during isometric or heterometric exercise [52], and a lower vasoconstrictive response to sympathetic activation during breathing-in [53]. Such a blunted sympathetic response or sympathetic reserve may promote weight gain and aggravate insulin resistance and subsequent hyperinsulinemia, and thus maintain the vicious circle of weight gain—insulin resistance—sympathetic activation with blunted response—weight gain, etc. Increased leptin secretion by the adipocytes in patients with obesity contributes to vascular and systemic insulin resistance and SNS dysfunction [3, 4]. In addition to being an important regulator of fat accumulation, food intake, neuroendocrine outflow and metabolism, leptin, an adipocyte-derived hormone, plays a role in the development of hypertension by increasing SNS activity in tissues involved in cardiovascular regulation such as the kidneys and blood vessels [54, 55]. Leptin has a key role in energy expenditure regulation through SNS, as it targets the arcuate nucleus to activate the concerned signalling pathways [47]. Impaired adiponectin secretion in patients with obesity is also thought to be involved in SNS activation and the promotion of insulin resistance [4]. Also, insulin-induced inhibition of lipolysis has been reported in obese patients with type 2 diabetes following modulation of SNS activity [37]. Results of animal and human studies suggest that central sympathetic overactivity is involved in the aetiology and complications of metabolic syndrome and its associated components (i.e., abdominal obesity, insulin resistance, hyperglycaemia, dyslipidemia, hypertension, systemic inflammation) [43].

Increased urinary noradrenaline and metabolite levels, and elevated plasma noradrenaline spill over, have been demonstrated in obese adults compared with lean individuals [56, 57]. Also, obese adults display increased resting sympathetic nerve activity in skeletal muscle [58–60]. Obesity is also associated with increased SNS activity to various tissues, in particular the kidneys, leading to increased vasoconstriction and fluid retention, and activation of the renin–angiotensin–aldosterone system, promoting increase in arterial blood pressure [55]. It is believed that these changes are mediated by elevated serum leptin levels due to increased fat mass combined with selective leptin resistance [55]. There is evidence that a reduction in body weight, induced by lifestyle

changes, can improve lipid profile, glucose metabolism, insulin sensitivity, and result in lowering systolic and diastolic blood pressure [61]. Some specialised diets have also been shown to reduce sympathetic activity, and improve baroreflex and insulin sensitivity [61]. In addition, both SNS and parasympathetic nervous system (PNS) activities are improved when dietary measures are combined with exercise [62]. Nevertheless, for patients with obesity-related hypertension (OHT) dietary measures are not sufficient to control blood pressure, and pharmacological strategies must be initiated [48].

OHT is often associated with diabetes mellitus, metabolic syndrome and dyslipidemia. Sympathetic overdrive in patients with OHT is often enhanced in those with a sleep apnea syndrome. Leptin, insulin and RAAS may contribute to increase SNS activity. Indeed, clamp studies in healthy and obese individuals have shown that hyperinsulinemia may activate the SNS and reduce PNS activity [63, 64], and so may promote OHT, and that hyperinsulinemia and inappropriate SNS activation contributes to increased renal sodium reabsorption [4]. Besides, in case of insulin resistance, a vascular resistance to the vasodilative effect of insulin is also observed promoting development of hypertension [64]. Similarly, endothelial dysfunction associated with obesity may impair the vasodilative effect of leptin and also contribute to hypertension [65] (Fig. 2).

In addition to sympathetic alterations, a cardiac vagal defect may be detected in more than one third of patients with metabolically healthy obesity [66], suggesting that vago-sympathetic imbalance is an early disorder in obesity which may play a role in subsequent hypertension. Indeed, rats with lesions of ventromedial hypothalamus do not exhibit hypertension despite massive obesity, increased plasma catecholamines and normal heart beta-adrenoceptivity. In this model, increased heart vagal tone was suggested to be protective against the development of hypertension [67].

GLP-1 and SNS overdrive

The SNS has also been implicated in the control of heart rate via glucagon-like peptide 1 (GLP-1), an incretin hormone released by the gut in response to food intake, which has receptors in peripheral tissues and central nervous system [47, 68, 69]. It is known that GLP-1 has beneficial effects on metabolic parameters in patients with type 2 diabetes such as increase in insulin release, replenishment of insulin stores, pancreatic β -cells proliferation, improvement of insulin sensitivity in skeletal muscle, inhibition of glucagon secretion, decrease in liver gluconeogenesis, decrease in gastric emptying, increase in thermogenesis, reduction of appetite and body weight [70, 71]. As well as glycemic control, GLP-1 plays a role in

heart rate control [72, 73], with animal studies suggesting that this GLP-1-mediated heart rate control is associated with sympathetic activation and/or depression of parasympathetic modulation [74–76] and that GLP1-receptor agonists induce an increase in heart rate [69]. In addition, animal studies suggest that GLP-1-enhances sympathetic activity and increases thermogenesis of brown adipose tissue [70]. However, a slight blood pressure decrease is observed during treatment by GLP1-receptor agonists, as a result of weight loss and possibly due other mechanisms including an improvement of endothelial function [77].

Sleep apnea and SNS overdrive

It has been suggested that activation of the autonomic system caused by baroreflex dysfunction, predisposes to hypertension in people with sleep apnoea, with more markedly impaired baroreceptor reflex sensitivity being significantly associated with increased blood pressure and hypertension in generally healthy elderly individuals with sleep apnea [78]. It has been postulated that the cardio-protective effects of parasympathetic activity are reduced by acute sympathetic activation related to the induction of a downwards resetting of baroreceptor by sleep apnoea [78]. Impaired baroreceptor reflexes and sympathetic hyperactivity have also been observed in heart failure, which is also closely associated with sleep apnea [79].

The increased sympathetic activity is seen in patient with sleep apnea even when they are awake, and the apneic episodes are associated with further increases in sympathetic nerve activity and blood pressure during sleep [80].

It has been shown that an increase in SNS activity is also responsible for an increase in insulin resistance and central adiposity, which are associated with higher rates of sleep apnea [81]. In obese patients with resistant hypertension and sleep apnea, a decrease in sympathetic overdrive leads to a significant weight loss and decrease in blood pressure [81]. Thus, it is justified to screen for sleep apnea in diabetic patients with resistant hypertension, even in absence of symptoms to optimize blood pressure reduction [82].

Evaluation of SNS activity

Several methods are available to measure SNS hyperactivity including sympathetic nerve recording, radiotracer-derived measurements of regional sympathetic neuronal activity or heart rate and blood pressure variability.

Microneurography

Microneurography consists in measurement of sympathetic nerve activity in the skin or in skeletal muscle

(MSNA) [83]. It is known that sympathetic outflows happen in bursts, so measuring sympathetic activity is based on detection of these bursts. Microneurography is an invasive method, needing a skilled technician to be performed [84].

The analysis can be made in three ways: measurement of the burst frequency (count of the number of bursts occurring/minute), measurement of burst incidence (number of bursts occurring per 100 heart beats) or measurement of the total neural activity (sum of bursts amplitude in 1 min) [31, 84, 85].

Radiotracer-derived measurements

As heart and kidneys are out of reach for microneurography, radiotracer-derived measurements have been developed. This method is based on the measurement of noradrenaline outflow to the circulation. Tritiated I-norepinephrine is infused in the patient's circulation, allowing to measure organ-specific noradrenaline spill over to plasma by isotope dilution [86, 87]. 123I-metaiodobenzylguanidine (123I-MIBG) is a norepinephrine analogue that can be used for non-invasive cardiac sympathetic neuronal activity assessment [88, 89].

Other methods

SNS activity can also be measured by indirect methods such as heart rate variability, blood pressure variability or arterial baroreflex sensitivity.

Heart rate variability

Heart rate variability (HRV) is the variation in time of the heart rate around the mean value of the patient between two heart beats. A decrease in the HRV is seen during SNS hyperactivity and is correlated with an increased risk of cardiac mortality and is a predictor risk factor for cardiovascular events [40].

It can be measured through a few-minutes or 24-h ECG recordings that can accurately sense RR intervals, and calculated using several indexes: Time domain indexes, Frequency indexes or nonlinear indexes [90]. HRV is also used to assess cardiac vagal tone [89, 91].

Blood pressure variability

Variability in blood pressure is classified as short-term, mid-term and long-term variability and increases according to conditions depending on sympathetic activity. Mid- and long-term variability can be measured through ambulatory BP monitoring [92] while short-term variability can be measured by spectral analysis of blood pressure measured using finger plethysmographic devices [93].

Arterial baroreflex sensitivity

Baroreflex sensitivity determines the capability of the SNS to respond to changes in blood pressure sensed at the level of the carotid sinus and aortic arch [94]. It can be measured by application of a neck chamber (stimulation of carotid baroreflex), the use of vasoactive drugs (detection of systemic pressure changes), and the Valsalva maneuver (to detect bradycardic responses). To determine baroreflex sensitivity, physicians must analyse the relation between diastolic blood pressure and MSNA [95, 96].

The neck chambers measure baroreflex sensitivity stretching and compressing the baroreceptors via negative and positive pressures applied to the anterior neck [97]. Injection of a vasoactive drug (angiotensin or phenylephrine) allows a recording of ECG and beat-to-beat arterial pressure [98].

Multiple studies have analysed cross-correlation between HR and BP variabilities, which may account for changes in the autonomic nervous activity [99, 100].

Effects of hypertension management strategies on the SNS

Recommendations for the treatment of hypertension include lifestyle changes (i.e., diet, weight loss, exercise) either alone or in combination with pharmacotherapies [1]. Reduction in sympathetic overdrive is expected to trigger a series of favourable cardiovascular and metabolic consequences [28], as shown with several of these hypertension management strategies.

Lifestyle modifications

Lifestyle changes are the first line of treatment for hypertension [1]. While exercise reduces blood pressure and is protective against CVD, it does not appear to affect blood pressure, lipid levels or risk of diabetes [39]. A high-protein specialised eating plan, the Dietary Approach to Stop Hypertension (DASH), with an emphasis on fruit and vegetables, low-fat dairy, wholegrain cereals, vegetables and nuts, lean meats, poultry and fish, has been shown to reduce blood pressure and lipid levels, and improve metabolic markers when used as part of a weight-loss program [38]. Additionally, weight loss has been shown to depress SNS activity, with resultant improvements in insulin clearance, and reduced peripheral vascular resistance [38]. Central sympathetic outflow has also been implicated in the physiology of salt-sensitive blood pressure changes [101], and high sodium intake is associated with parasympathetic inhibition, dyslipidemia and inflammation in patients with mild hypertension [102].

In the CALERIE trial (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) [62],

patients were divided in three groups: calorie restriction (decrease of 25% of energy intake), calorie restriction and exercise (decrease of 12.5% associated with an increase of 12.5% in energy expenditure) or low-calorie diet until decrease of 15% of weight, followed by weight maintenance. After 6 months of trial, in all groups, the SNS activity was decreased whereas the PNS was increased but the changes reached significance only in the second group. Therefore, the results suggest that weight loss is an important factor to improve the SNS/PNS balance, especially when calorie restriction is combined with exercise.

Catheter-based renal denervation

Catheter-based renal denervation has been explored as a treatment for drug-resistant hypertension [103, 104]. Renal denervation decreased blood pressure and reduced cardiovascular morbidity [105, 106]. As well as the effects on blood pressure, renal denervation has demonstrated a decrease in muscle sympathetic nerve activity with a reduction of SNS-mediated effects such as improved glycaemic control and insulin resistance, and decreased total peripheral resistance [103, 104, 107]. Observed positive effects of renal denervation on the cardiovascular system include reduced arterial stiffness (lower pulse wave velocity), reduced left ventricular mass, improved heart failure symptoms and diastolic function, and increased left ventricular ejection fraction [103, 107]. Heart rate is also significantly reduced through renal denervation [108]. With regards to the effects on the kidney, renal denervation has been shown to reduce renal noradrenaline spill over and plasma renin release [109]. Interestingly, a recent paper showed that a baseline 24-h heart rate above the median (73.5 bpm), suggesting a higher sympathetic activity, predicted greater BP reductions after renal denervation and may allow physicians to select patients likely to respond to the procedure [108].

Pharmacological strategies

Several pharmacological strategies can be set up to decrease blood pressure, targeting either RAAS (angiotensin converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs)), cardiac output (β -blockers), peripheral vascular resistance (calcium channel blockers (CCB) or sodium reabsorption (diuretics)).

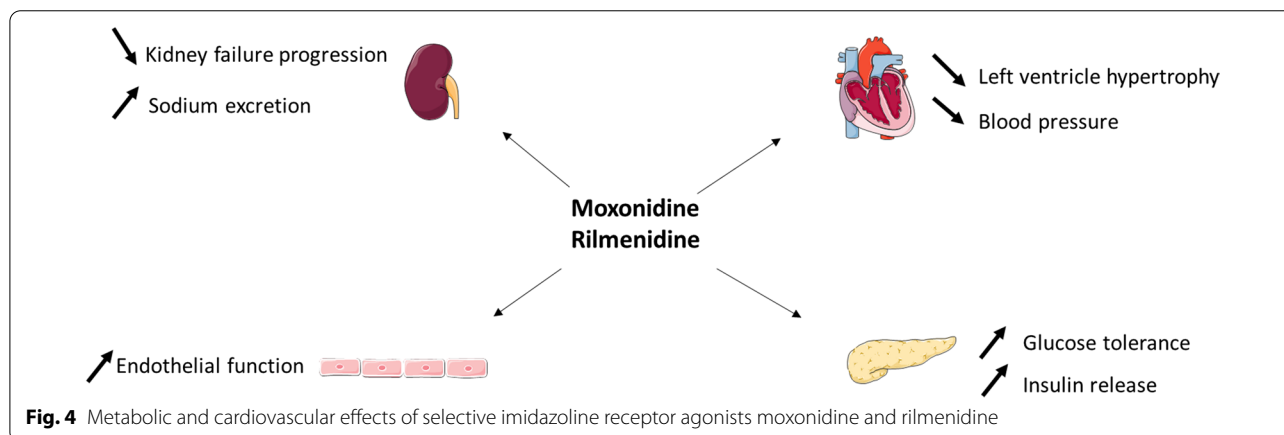
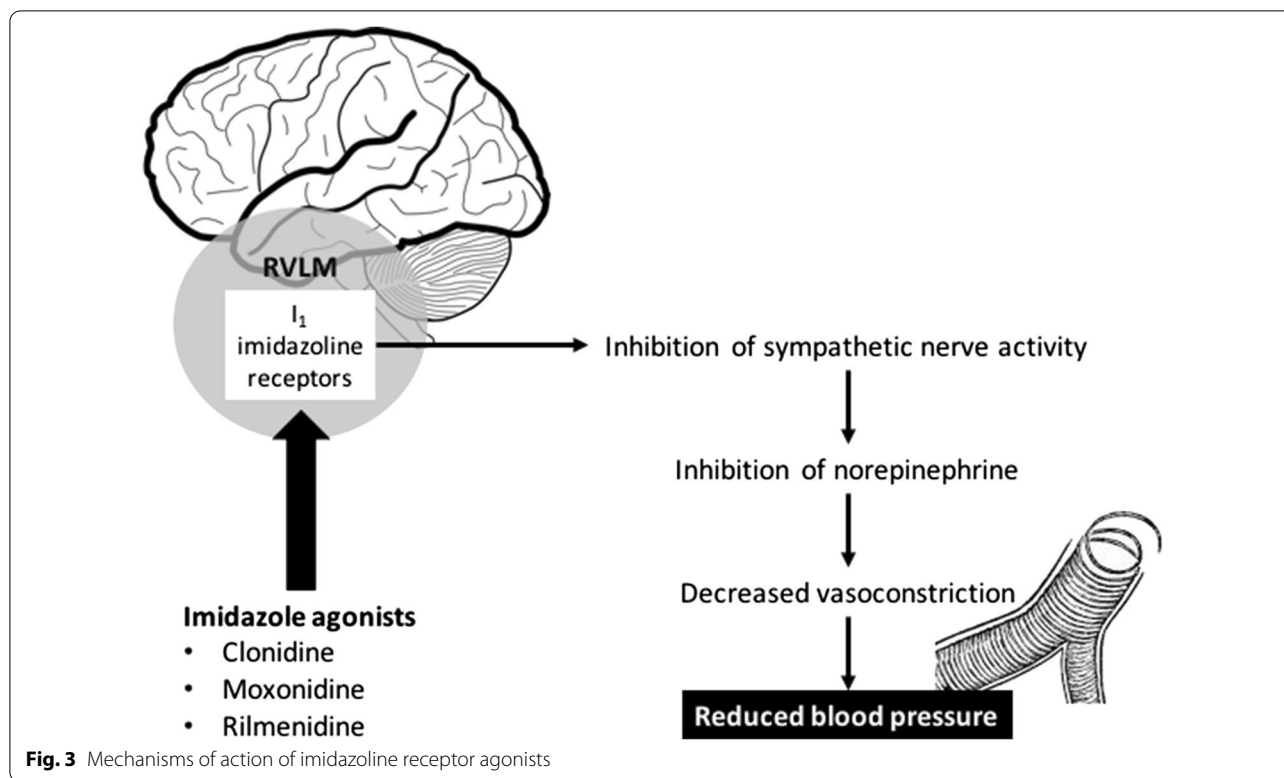
Pharmacological therapies for the management of hypertension via inhibition of the SNS include β -blockers and imidazoline receptor agonists, targeting β -adrenergic and imidazoline I_1 receptors, respectively [9, 10]. While ACEis and ARBs act by antagonising the renin–angiotensin–aldosterone system, they appear to have little or no effect on the SNS [110, 111].

Beta-blockers

β -blockers, also indicated for the treatment of heart failure [79, 112], decrease SNS activation by antagonising β -adrenergic receptors [10], and have potential beneficial effects on cardiac fibrosis. While they reduce SNS activation and cardiovascular outcomes in patients with heart failure and reduced LV ejection fraction, they also have unwanted negative metabolic effects including insulin resistance, dyslipidemia and reduced glycaemic control [10, 31, 113]. They also increase weight gain [2, 48].

Selective imidazoline receptor agonists.

Imidazoline receptor agonists (e.g., clonidine, moxonidine, rilmenidine) act on the imidazoline I_1 receptor [9]. Concentrated within the rostral ventrolateral medulla (RVLM), a part of the brainstem involved in sympathetic control of blood pressure, imidazoline I_1 receptors are important for the regulation of sympathetic drive [114, 115]. It is believed that the I_1 receptor may belong to the neurocytokine receptor family, since its signalling pathways are similar to those of interleukins [114]. Of the imidazoline agonists, clonidine stimulates both α_2 receptors and imidazoline I_1 receptors, whereas moxonidine and rilmenidine are considered as selective imidazoline receptor agonists (SIRAs), activating only imidazoline I_1 receptors within the RVLM [9, 116], avoiding thus side effects seen with clonidine (mainly tiredness, drowsiness and sedation). Increased neuronal activity in the RVLM by direct stimulation of I_1 receptors by imidazoline agonists decreases sympathetic outflow, resulting in a fall in blood pressure (Fig. 3) [115]. I_1 receptors are also localized on the plasma membrane of the neurons of the adrenal medulla, renal epithelium, pancreatic islets, platelets, and the prostate [114, 117]. In line with these findings, rilmenidine has demonstrated inhibition of cardiac baroreflex sympathetic activity, with subsequent reduction in heart rate [118], and beneficial effects of moxonidine include enhanced sodium excretion, improved insulin resistance (clamp study) [119] and glucose tolerance and protection against hypertensive target organ damage (e.g., kidney disease, cardiac hypertrophy) [120]. Moxonidine was also shown to decrease kidney failure progression, reduce left ventricular hypertrophy and to improve endothelial function (first step to atherosclerosis development) in hypertensive patients [116, 120]. In the MERSY study [121] administration of moxonidine daily (0.2–0.4 mg) for 6 months as monotherapy or in combination with another antihypertensive treatment in hypertensive patients with a metabolic syndrome was shown to improve blood pressure control, to reduce the body weight and to act on metabolic parameters as lipid fractions and fasting plasma glucose (Fig. 4). Recently,



an international real-world medical research shown that in the surveyed countries, physicians considered SIRAs as a useful therapeutic option, frequently prescribed for hypertensive patients with metabolic outcomes [122].

Conclusions

Hypertension is a multifactorial disease process that is a well-established cardiovascular risk factor. Overactivation of the SNS plays a central role in the aetiology of hypertension and has also been linked to several comorbidities commonly associated with hypertension, as

metabolic syndrome, diabetes mellitus, dyslipidemia or sleep apnea syndrome. Some of the treatments for hypertension, particularly selective imidazoline receptor agonists, target the SNS and have demonstrated beneficial cardiovascular, renal, and metabolic effects in addition to lowering blood pressure.

Abbreviations

SNS: Sympathetic nervous system; CVD: Cardiovascular diseases; ANS: Autonomic nervous system; RAAS: Renin–angiotensin–aldosterone system; PNS: Parasympathetic nervous system; GLP-1: Glucagon-like peptide 1; MSNA: Muscle sympathetic nerve activity; DASH: Dietary Approach to Stop Hypertension;

CALERIE: Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; CCB: Calcium channel blockers; RVLm: Rostral ventrolateral medulla; SIRAs: Selective imidazoline receptor agonists.

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Competing interests

Paul Valensi discloses the following potential conflicts of interest: lectures for Abbott, AstraZeneca, Bayer, Lilly, Hikma Pharmaceuticals, Merck Sharp & Dohme, Novo Nordisk, Novartis, Pfizer, Sanofi; research grants from Abbott, Bristol-Myers-Squibb–AstraZeneca, Novo Nordisk; participation in expert committees for AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Lilly, Novo Nordisk, Sanofi, Servier, Stendo.

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