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Hypertensive subjects with type-2 diabetes, the sympathetic nervous system, and treatment implications

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ABSTRACT

Central obesity is closely linked to hypertension and type-2 diabetes (DM2) in young/middle-age. In the elderly, systolic hypertension is a reflection of aging/stiff arteries. Diastolic (±systolic) hypertension in young/middle-age is accompanied by increased sympathetic nerve activity, particularly in the presence of the metabolic syndrome or DM2. High beta-receptor density (Bmax) and cyclic AMP (cAMP) levels in human lymphoctes, independent of blood pressure, are associated with a high risk of myocardial infarction (not stroke-risk, which is dependent on blood pressure). This has treatment implications in the young/middle-aged hypertensive subject. Antihypertensive agents that increase sympathetic nerve activity e.g. dihydropyridine calcium blockers, angiotensin receptor blockers, and thiazide-type diuretics, do not reduce (and may increase) the risk of myocardial infarction. Beta-1 blockade, effective in reversing and stabilising coronary atheromataous plaque, and with possible anti-tumor properties, is superior to ACE-inhibition, and is the treatment of choice in young/middle-aged hypertension with DM2.

1. Introduction

High blood pressure is number one global risk factor for premature death, being ahead of smoking and high cholesterol [1]. Closely allied to the global problem of hypertension is the "epidemic" of overweight/obesity. The nine countries of Oceania have the highest body mass index (BMI) in the world, being an average of 35.0 kg m^2 for women and 33.9 kg m^2 for men [2]. The highest BMIs within developed countries are in the USA [2], where 66% of adults are overweight/obese (BMI > 25 kg/m^2) [3]. The UK [4] and Australia [5] are not far behind where about 60% of the adult population are overweight/obese. Worryingly the obesity problem is also affecting children [3,4,6].

Obesity, particularly central/abdominal, is closely linked to hypertension and type-2 diabetes (DM 2) [7,3]. Hypertension is twice as frequent in patients with DM2 [8]. Such patients are at high risk of premature coronary heart disease [9,10], with massive economic consequences [11]. Indeed, the prognosis of such subjects is similar to individuals with a previous myocardial infarction [12]. The outlook is particularly bleak for patients with a normal BMI plus central obesity i.e. normal weight central obesity [13].

It has been noted that patients with DM2 with hypertension have markedly raised sympathetic nerve activity [8]. Such patients have a particularly increased renal and cardiovascular risk profile [7].

The aim of this review is 1. To examine the pathophysiology of essential hypertension in young/middle-aged hypertensive subjects with type-2 diabetes (DM-2), paying particular attention to the interrelationship between obesity (especially central obesity) and the sympathetic nervous system 2. To discuss appropriate anti-hypertensive therapeutic options in such subjects.

2. Search Strategy

Involved utilisation of the Cochrane Library and PubMed search under the terms — hypertension AND diabetes; hypertension AND sympathetic nerve activity; diabetes AND sympathetic nerve activity; treatment AND hypertension plus diabetes. The search extended to July 2013, and imposed no language restrictions.

3. Pathophysiology of essential hypertension (with and without the metabolic syndrome or DM2)

3.1. Genetic component

The development of essential hypertension is linked to various combinations of genetic and environmental factors. Studies on twins and adopted children indicate that genetic factors account for about 30% of cases of essential hypertension [14]. Thus hypertension is more common in individuals with a positive family history. Twenty eight genes have so far been detected that contribute to blood pressure variation, albeit in most cases to a fairly limited extent [15].

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3.2. Environmental aspects

Lifestyle factors are responsible for 70%–80% of cases of essential hypertension, and include overweight, physical inactivity, high salt intake, alcohol abuse, and the typical western diet low in fruit, vegetables and fish, but high in high in saturated fat and sugar [16]. However overweight/obesity is undoubtedly the dominant factor, not only in adults but also in children [17].

The Framingham Group [18] showed that in an initially healthy population, a) the development of diastolic (± systolic) hypertension occurred in the young/middle-aged and was closely linked to overweight/obesity, b) the development of isolated systolic hypertension occurred in the elderly and was a function of aging and stiffening of the arteries — Table 1. Others [19–21] have confirmed the association between obesity and hypertension in the young/middle-aged, and that central obesity was the important component [22]. Central obesity is linked not only to hypertension in the young/middle-aged, but also to a high heart rate and cardiac output [23], suggesting increased sympathetic nerve activity. The Framingham Group [23] has also noted that the development of hypertension over a 28 year follow-up period, in a young/middle-aged group, was associated with an increase in resting heart rate (a surrogate for high sympathetic nerve activity).

3.3. Obesity, metabolic syndrome, DM2, and hypertension in the young/middle-aged, and increased sympathetic nerve activity

Obesity, particularly central, is linked to increased muscle sympathetic nerve activity [24] — Fig. 1. In men there is a powerful positive linear relationship between waist circumference and sympathetic nerve activity [25].

Though in normal-weight young/middle-aged hypertensives sympathetic nerve activity is raised (vs normotensive controls) [26], it is less than in age-matched obese hypertensive subjects [27]. It is therefore not surprising that in patients with the metabolic syndrome [28], DM2 [29], where central obesity is very common, there is a marked increase in sympathetic nerve activity — Fig. 2. The increased sympathetic nerve activity is greatest where the metabolic syndrome, or DM2, is combined with hypertension [28,29]; hypertension is more common in subjects with DM2 than in the normal population, the prevalence being 40%–80% [30]. The increased sympathetic nerve activity, as expressed by increased arterial norepinephrine (noradrenaline) levels, is significantly greater in cases of DM2 (13 out of 17 were hypertensive) than the metabolic syndrome (10 out of 17 were hypertensive) [31].

Thus, in younger/middle-aged subjects, the metabolic syndrome, DM2, and hypertension have obesity and raised sympathetic nerve activity in common. This has important therapeutic implications (see later).

3.4. The link between central obesity and increased sympathetic nerve activity in the young/middle-aged hypertensive subject

The likely series of events linking central obesity with high sympathetic nerve activity and hypertension have been described [32]. Briefly,

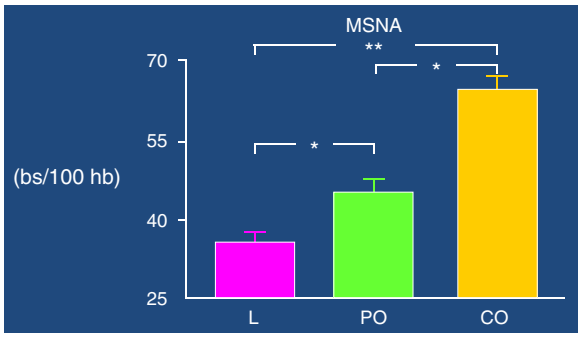

Fig. 1. In 30 lean (L), 20 peripherally obese (PO) and 26 centrally obese (CO) subjects (mean age 36 years), muscle sympathetic nerve activity (MSNA) was significantly higher in CO than PO and L subjects. Grassi G et al. 2004.

centrally located adipocytes produce several vasculotoxic adipokines and cytokines e.g. tumor necrosis factor (TNF-alpha) and interleukin-6 (IL-6), which act upon the liver, resulting in release of C-reactive protein (CRP), an indicator of acute inflammation. Endothelial/hepatic inflammation leads to an insulin-resistant state, resulting in increased insulin secretion. High insulin levels, in addition to high leptin levels (produced mainly by central adipocytes), act upon the hypothalamic region of the brain resulting in increased sympathetic outflow and renin release (via beta-1 stimulation of the renal juxta-glomerular apparatus). High renin levels result in angiotensin II production, which (like leptin and insulin) acts centrally, resulting in increased sympathetic outflow.

The whole process is illustrated in Fig. 3, which also indicates the results of chronic beta-1 stimulation upon the periphery, and the theoretical benefits of beta-1 blockade. It is of interest to note that in obesity-related hypertension (in rabbits), antagonists of insulin, and particularly of leptin, administered intra-cerebrally, result in a reduction of renal sympathetic nerve activity and significant falls in blood pressure of 9% with the leptin antagonist and 5% with the insulin antagonist [33].

4. Elderly systolic hypertension and the sympathetic nervous system

With increasing age, muscle sympathetic nerve activity increases in both normotensive and hypertensive subjects [34], particularly in women [35]. In contrast, unlike muscle sympathetic nerve activity, renal sympathetic outflow (norepinephine) decreases with age [36]. As age increases, beta-receptor affinity/sensitivity declines [8–37], resulting in a fall in cardiac output [39]. The loss of beta-receptor affinity/sensitivity in the kidney results in a fall in renin–angiotensin activity (stimulation of beta-1 receptors in the juxta-glomerular apparatus results in a release of renin). The combination of reduced renin–angiotensin activity and reduced beta-1 sensitivity would account for the salt retention noted in elderly systolic hypertension [40].

As the sympathetic nerve activity has a minor, or no, role to play in the development and maintenance of elderly systolic hypertension, there will be no further reference to the elderly.

Table 1
Different Predictors of Diastolic Hypertension (DH) (raised systolic — SDH) and Isolated Systolic Hypertension (ISH) — FRAMINGHAM Study.

Predictors of Diastolic Hypertension (Systolic Hypertension) = DBP ≥ 90 mmHg (SBP ≥ 140 mmHg)	Predictors of Isolated Systolic Hypertension = SBP ≥ 140 mmHg + DBP < 90 mmHg (wide P-P)
1. Young age	1. Older age
2. Male sex	2. Female sex
3. High BMI at baseline	3. Increased BMI during follow-up (weak)
4. Increased BMI during follow-up	4. ISH arises more commonly from normal and high normal BP, than "burned out" diastolic hypertension
5. Main mechanism of DH and SDH is raised peripheral resistance	5. Only 18% with new-onset ISH had a previous DBP ≥ 95 mmHg
	6. Main mechanism of ISH is increased arterial stiffness = aging of arteries