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ORIGINAL ARTICLE

# Hypertension, single sugars and fatty acids

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**Macronutrients may induce various hemodynamic effects. In the fructose-fed rat blood pressure increase is associated with insulin resistance and enhanced sympathetic activity. In humans, oral glucose intake induces a slight and transient increase of blood pressure secondary to sympathetic activation. This increase may be higher in hypertensive subjects and followed by a significant fall in blood pressure in elderly subjects. Saturated fatty acid-enriched diet induces in male rats a significant increase in blood pressure related to sympathetic activation. Some observational and interventional studies suggest that *n*-3 polyunsaturated fatty-acids may reduce blood pressure in humans. Thus, both carbohydrates and fatty acid balance may contribute to blood pressure changes. The clinical relevance of these data should be evaluated in long-term trials, in particular in overweight and hypertensive subjects.**
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## Introduction

Hypertension is more prevalent among overweight people and may result from various mechanisms including insulin resistance, hyperinsulinaemia and, increased sympathetic activity.[1–4] Changes in food habits are also likely to contribute to the increase in blood pressure even before weight gain. The increase in caloric intake induces an augmentation of plasma catecholamines, which results from sympathetic activation.[5,6] These changes are accompanied by an increase in serum insulin and insulin resistance. The increase in serum insulin levels is probably involved for the most part in sympathetic activity enhancement, as suggested by the activation of the sympathetic nervous system during a euglycemic hyperinsulinaemic clamp.[7]

Macronutrients induce various haemodynamic changes. In this review, we examine the acute and long-term effects of single sugar and fatty-acid intake in rats and humans. Since overweight subjects are more susceptible to hypertension, we will also address the question of whether some of these effects might be relevant, in particular, to patients who are overweight and/or show insulin resistance.

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### Haemodynamic effects of carbohydrates

*Experimental data*
Reaven *et al* have carried out a series of works investigating the occurrence of insulin resistance and the changes in blood pressure after single-sugar intake in rats. The introduction of fructose induces, within 10–15 days, insulin resistance, compensatory hyperinsulinaemia and a rise in blood pressure.[8,9] The introduction of glucose or sucrose in the diet without increase in total caloric intake during 2 weeks induces an increase in serum insulin without change in blood glucose, an increase in serum triglycerides and blood pressure, the latter being higher after sucrose.[10] The hypertensive effect of fructose has even been shown to be higher in rats with spontaneous hypertension.[11]

Kaufman *et al*[12] have compared the effects of diet enrichment in glucose or fat on body weight and blood pressure in normal rats. Blood pressure increased more in these rats than in normally-fed rats, whereas body weight increased similarly in glucose-fed rats as in those with a normal diet but less than in those with a fat-enriched diet.

Sympathetic activation and changes in endothelium function may be involved in the increase in blood pressure. In rats under a glucose-enriched diet, urine noradrenaline is increased as compared with rats under a normal diet.[12] In fructose-fed rats, sympathectomy prevents hyperinsulinaemia and hypertension.[13] In rats receiving fructose, rilmenidine, a central antihypertensive agent that acts

through $I_1$-medullar receptors of imidazoline, prevents the increase in body weight induced by fructose. Blood glucose, free fatty acids and glucose utilization become similar to that in control rats. This suggests that rilmenidine may improve the deleterious effect of fructose, in particular, on blood pressure and insulin resistance, by reducing sympathetic activity.[14] Thus, sympathetic activity is likely to play a central role in the occurrence of insulin resistance associated with single sugar enrichment. The increase in serum insulin secondary to insulin resistance is likely to contribute to sympathetic activation and the rise in blood pressure elicited by sugars.

Endothelium dysfunction has been clearly shown to be associated with obesity and insulin resistance. Insulin *per se* induces vasodilation by activating NO-synthase and nitric oxide (NO) production in smooth muscle cells. Endothelium dysfunction associated with insulin resistance may contribute to hypertension. The contribution of NO production in the prevention of hypertension in normal rats receiving a prolonged glucose infusion during 7 days has been tested using a previous treatment by L-NAME, an arginine antagonist that reduces NO synthesis. This treatment amplifies the increase in blood pressure induced by glucose infusion.[15] These data confirm the hypertensive effect of glucose and show that NO may minimise these effects. On the contrary, the hypertensive effect of glucose might be amplified if endothelium function is impaired. In addition, since NO depresses sympathetic activity, endothelium dysfunction might also elevate blood pressure by exaggerating glucose-induced sympathetic activation. Indeed alpha- and beta-adrenergic blockade prevents partly the deleterious effect of L-NAME combined with glucose on blood pressure.[16] Thus, the protective effect of NO against glucose-induced hypertension might be mediated by its depressive effect on sympathetic activity.

*Data in humans*

The intake of 100 g glucose has been shown to induce an acute moderate elevation (7 mmHg) in systolic blood pressure and a significant increase in heart rate.[17] We have studied the effect of 75 g glucose intake in middle-aged normal adults and observed a slight and sustained acceleration of heart rate (5 beats/min) without any significant change in mean blood pressure.[18] After a meal enriched in carbohydrates (85% of caloric intake), a significant increase in heart rate has been reported, whereas blood pressure decreased significantly by 30 min. The early increase in peripheral blood flow may have limited the increase in blood pressure.[19]

The role of sympathetic activity in the haemodynamic changes induced by carbohydrates has been investigated by various methods including serum catecholamine measurement, muscle sympathetic activity recording, and the analysis of heart rate and blood pressure variations.

Serum noradrenaline level and muscle sympathetic activity increase significantly after glucose intake, and a significant correlation has been reported between muscle sympathetic activation and serum insulin.[17]

In our experiment, sympathetic activation as evidenced by the increase in the low-frequency/high-frequency spectra ratio provided by spectral analysis of heart rate variations was probably involved in the late heart rate acceleration and might have limited the trend to a late hypotension related to splanchnic vasodilation and the peripheral vasodilation induced by insulin response.

Sympathetic activation together with vagal activity depression provoked by serum insulin increase[20] may be suspected to increase blood pressure in patients with basal hyperinsulinaemia, that is, overweight or hypertensive patients. Indeed, we have previously suggested that a high vagal activity may be protective against hypertension associated with obesity.[21] Since cardiac vagal activity is often depressed in overweight and hypertensive subjects,[22,23] the repetitive sympathetic activation induced by single-sugar intakes might together with vascular insulin resistance (resistance to the vasodilative effect of insulin) contribute to the elevation of blood pressure. However, this hypothesis should be tested in long-term experimental settings in humans. It may be mentioned that in nondiabetic overweight subjects an association was found between cardiac parasympathetic dysfunction and a higher long-term carbohydrate intake.[24]

*Effects of carbohydrates on blood pressure in particular situations*

Oral glucose intake has been shown to be followed by a significant acute increase in systolic blood pressure in a series of 40 subjects, 15 of them with moderate hypertension and 13 with glucose intolerance. Unfortunately, the data in the hypertensive subgroup have not been isolated.[25] Whether the effect of glucose on blood pressure increase is higher in hypertensive subjects than in subjects with normal blood pressure should be tested specifically.

We have analysed the haemodynamic changes after glucose intake in subjects older than 70 years and found a transient increase in blood pressure followed by a significant decrease (by 20 mmHg) without concomitant changes in heart rate or vagosympathetic activity. The lack of sympathetic activation might contribute to postprandial hypotension and dizziness induced by single sugars in some elderly subjects. In the same subjects, we have analysed haemodynamic parameters after a mixed meal. Blood pressure and heart rate changes were quite similar in these subjects and in younger ones.[18] Therefore glucose intake at variance with a mixed meal may induce in the elderly an inappropriate haemodynamic response with secondary hypotension.

### Effects of fatty acids

*Epidemiological data*

Several epidemiological studies have suggested that the risk for coronary heart diseases is increased by saturated fatty-acids and decreased by mono and polyunsaturated fatty-acids (for a review, see[26]). Some studies have also reported interesting data regarding the link between fatty acids and blood pressure. In a cross-sectional Finnish study, mean blood pressure was associated with dietary intake of saturated fats and inversely with dietary intake of linolenic acid.[27] In the Health Professionals Follow-up Study, there was no significant association between fatty acids and incident hypertension after adjustment for other risk factors.[28] In the Paris Prospective Study II, the level of palmitoleic acid (a monounsaturated fatty acid) in serum cholesterol esters, which is supposed to reflect dietary saturated fats (since there is considerable mono-unsaturated endogenous synthesis from saturated fat), was associated with hypertension.[29] According to the ARIC (Atherosclerosis Risk In Communities) study, fatty-acid composition in plasma cholesterol esters has been associated with the 6-year incidence of hypertension. The results suggest that a lower plasma linoleic acid level and higher plasma levels of palmitic and arachidonic acids are associated with a higher risk of hypertension.[30] Arachidonic acid may act through changes in eicosanoid/prostaglandin metabolism, and the balance between thromboxan-$A_2$ (a vasoconstrictor agent) and prostacyclin (a vasodilating agent).

*Experimental data in rats*

Some experiments have tested the effect of lard on blood pressure in normal or castrated rats. In males a lard-enriched diet (50% of the energy content) induced a significant increase in blood pressure. However, this effect depends on gonadal function. Indeed, blood pressure increase in males was suppressed by castration and restored in castrated rats receiving testosterone supplementation. Moreover, in females lard did not induce any change in blood pressure but an increase was observed in ovariectomized females treated with testosterone.[31] Therefore, the effect of lard on blood pressure in rats depends on testosterone. In addition, Gerber *et al*[32] have shown that the sensitivity of small mesenteric arteries to noradrenaline is enhanced and endothelium function impaired in virgin rats fed with saturated fat (20% of energy content). Previous studies have reported an activation of sympathetic nervous activity in rats fed with saturated fat.[33] The impairment of insulin sensitivity in these rats together with a compensatory increase in serum insulin are likely to contribute to sympathetic activation and blood pressure increase.

*Human studies*

A decrease in blood pressure has been observed in hypertensive subjects after *n*-6 polyunsaturated-enriched diet. Several studies have provided evidence for protective effects of *n*-3 polyunsaturated fatty-acids against cardiovascular events and coronary restenoses. Rousseau *et al*[34] have reported that dietary *n*-3 polyunsaturated fatty-acid supplement reduces the increase in heart rate and blood pressure associated with psychological stress in rats. Similar protective effects against the rise in systolic blood pressure were found in spontaneously hypertensive rats, in rats with renovascular hypertension as well as in a hyperinsulinic rat model.[35,36] Some trials have tested the effects of *n*-3 fatty acids on blood pressure in man.

Cobiac *et al*[37] have shown that 6 g fish oil lowered blood pressure only in hypertensive subjects who consumed less than three fish meals per week. Morris *et al*[38] have reported the results of a meta analysis of 31 placebo-controlled trials including a total of 1356 subjects. After 3–24 weeks, fish oil consumption is accompanied by a blood pressure decrease. The authors were able to calculate that a supplement of 7.7 g *n*-3 fatty acids per day may lower systolic and diastolic blood pressure by 4 and 3 mmHg, respectively, in hypertensive patients.[38] Some moderate effects on blood pressure were also reported among hypercholesterolaemic patients and patients with cardiovascular disease, but little or no effect was reported among healthy normotensive subjects.

Many mechanisms may be involved in the beneficial effects of *n*-3 polyunsaturated fatty-acids on blood pressure. They improve membrane cell fluidity and prostanoic balance in favour of arterial dilation (EPA stimulates the synthesis of prostacyclin and inhibits the synthesis of thromboxan-A2). They also improve endothelium function and reduce cardiac adrenergic activity.

## Conclusion

In conclusion, both carbohydrates and fatty acid balance may contribute to blood pressure changes. The experimental data on blood pressure increase are more convincing in rats than in humans. Sympathetic activation and endothelium impairment are likely to play an important role in these effects. Single sugars may induce a moderate and transient increase in blood pressure in healthy subjects but possibly more important effects in elderly subjects, and in patients with hypertension and/or overweight. Besides their atherogenic consequences, high saturated-fat diet may contribute to hypertension whereas polyunsaturated *n*-3 supplements seem to decrease blood pressure in hypertensive patients. Finally, there is lack of strong evidence for the relation between macronutrients and blood pressure over days or weeks. More human

clinical data are required to address the effects of various macronutrients on blood pressure through long-term trials, in particular, in overweight and hypertensive subjects. Such effects should also be tested in patients receiving antihypertensive treatments.

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