Hemodynamic changes in postprandial state

P Valensi, E Cosson

SUMMARY
Several experimental data suggest that single sugar intake may induce heart rate acceleration and blood pressure elevation as a result of sympathetic activation secondary to insulin response and from alterations in endothelial function due to activation of oxidative stress. These hemodynamic effects might be more marked in patients with arterial hypertension or metabolic disorders, in particular in hypertensive patients with diabetes. A high-fat load may also induce activation of oxidative stress and endothelial dysfunction. However, the long-term effect of repeated intake of single sugar and fat on blood pressure, oxidative stress, and endothelial function should be tested in controlled trials. On the contrary, a balanced mixed meal (50% carbohydrates) does not induce any significant blood pressure changes. Nevertheless, acarbose treatment is able to reduce hypertension incidence in patients with impaired glucose tolerance and to improve endothelial function. In elderly subjects, in particular with type 2 diabetes or with severe dysautonomia, single sugar intake may account for nonhypoglycemic postprandial dizziness.

Key-words: Blood pressure · Postprandial blood glucose · Oral glucose load · Fat load · Endothelial function · Sympathetic activity · Cardiovascular risk.

RéSUMÉ
Modifications hémodynamiques en période postprandiale
De nombreuses données expérimentales suggèrent que la prise orale de sucres simples peut induire une accélération cardiaque et une élévation tensionnelle en relation avec une activation sympathique secondaire à la réponse insulinaire et une altération de la fonction endothéliale par une activation du stress oxydant. Ces effets hémodynamiques pourraient être plus amples chez les patients hypertendus ou présentant des désordres métaboliques, en particulier chez les diabétiques hypertendus. Une charge orale en lipides peut aussi induire une activation du stress oxydant et une dysfonction endothéliale. Les effets à long terme des ingestions répétées de sucres simples et de lipides sur l’élévation tensionnelle, le stress oxydant et la fonction endothéliale, doivent cependant être testés dans des essais contrôlés. Au contraire, un repas mixte équilibré comprenant 50 % de glucides n’induit pas de modification tensionnelle significative. Toutefois, un traitement au long cours par l’acarbose est capable d’améliorer la fonction endothéliale et de réduire l’incidence de l’hypertension artérielle chez des sujets intolérants au glucose. Chez les sujets âgés, en particulier chez les diabétiques de type 2, comme chez les patients avec dysautonomie sévère, la prise de sucres simples peut rendre compte de malaises postprandiaux non hypoglycémiques.

Mots-clés: Pression artérielle · Glycémie postprandiale · Charge en glucose · Charge lipidique · Fonction endothéiale · Activité sympathique · Risque cardio-vasculaire.

Address correspondence:
P Valensi, Service d’Endocrinologie-Diabétologie-Nutrition,
Hôpital Jean-Verdier, 93140 Bondy.
e-mail: paul.valensi@jvr.aphp.fr
Introduction

Several epidemiological data suggest the deleterious influence of postprandial glycemia on cardiovascular prognosis [1, 2]. A correlation has also been reported between postprandial glucose and some surrogate markers of cardiovascular risk [3, 4]. Various hemodynamic changes occur in the postprandial state and may contribute to alter the cardiovascular prognosis. These changes have been studied in experimental settings in rodents and also in healthy subjects, and evoke the role of some nutrients. They might be more important in patients with metabolic disorders. Improving the knowledge of such changes should lead to advise diet modifications and to offer treatments able to limit the meal-induced deleterious hemodynamic consequences.

Hemodynamic effects of carbohydrates and fatty acids in rats

A diet enrichment in fructose, glucose or sucrose induces insulin resistance and a rise in blood pressure within 10-15 days [5-8]. Sympathetic activation may be involved in the increase in blood pressure and insulin resistance. Indeed in fructose-fed rats sympathectomy prevents hyperinsulinemia and hypertension [9]. In addition, rilmenidine, a central anti-hypertensive agent which acts through 11-medullar receptors of imidazoline, reduces the increase in body weight and normalizes blood glucose, free fatty acids and glucose utilization [10].

Endothelium dysfunction associated with insulin resistance may also contribute to hypertension. A treatment by L-NAME, an inhibitor of NO-synthase, has been shown to amplify the increase in blood pressure induced by glucose infusion [11], which indicates that nitric oxide may minimize the hypertensive effect of glucose. In addition, alpha- and beta- adrenergic blockade partially prevents the increase in blood pressure induced by glucose combined with L-NAME [12]. Therefore the protective effect of nitric oxide against glucose-induced hypertension might be explained by its depressive effect on sympathetic activity.

As to the effect of fatty acids on blood pressure, a lard-enriched diet induces a significant increase in blood pressure in male rats, while this effect is suppressed by castration [13]. Saturated fat has also been reported to induce an activation of sympathetic nervous system [14]. The impairment of insulin sensitivity and the compensatory increase in serum insulin are likely to contribute to sympathetic activation and increase blood pressure. On the contrary n-3 polyunsaturated fatty acid supplement reduces the increase in blood pressure in several models of experimental hypertension [15, 16].

Hemodynamic changes induced by oral glucose intake in healthy humans

Acute hyperglycaemia induced by glucose infusion provokes an increase in blood pressure in healthy subjects that correlates with the increase in serum nitrotyrosine concentration. This data is consistent with the role of oxidative stress in blood pressure increase [17]. During a hyperglycemic clamp, serum ICAM-1 (intercellular adhesion molecule-1) levels elevate and this rise is maintained during a longer time if hyperinsulinemia is suppressed by octreotide [18], which stands in favour of an effect of hyperglycaemia on endothelium activation.

Several publications have provided evidence for an increase in blood pressure after oral glucose intake. After 100 g glucose taken orally, systolic blood pressure increases of 7 mmHg in means and there is an average heart rate acceleration of 7 beats/min [19].

Serum noradrenaline levels and muscle sympathetic activity increase significantly after oral glucose intake, and the increase in muscle sympathetic activity correlates with serum insulin response [19]. In addition modest acute hyperinsulinemia (up to 85 μU/ml) obtained during euglycemic hyperinsulinemic clamps in healthy subjects has been shown to induce both an increase in sympathetic activity and a depression in cardiac vagal activity [20]. The changes in vagosympathetic balance induced by insulin response to oral glucose are likely to play a major role in the increase in blood pressure.

Altogether, these data strongly suggest that the rise in blood pressure after oral glucose intake may result from vagosympathetic changes induced by insulin response and the induction of oxidative stress induced by hyperglycemia (figure 1).
Cardiac repolarization is also modified during acute hyperinsulinemia as evoked by hyperglycemic clamps. QTc interval is significantly lengthened after 2 hours of hyperglycemic clamp in healthy subjects [21]. Again sympathetic activation is likely to be involved in these changes of cardiac repolarization.

On the contrary, after a meal rich in carbohydrates (85% of the total energy intake), mean arterial blood pressure decreases and heart rate increases. The reduction in blood pressure is likely to result from splanchnic and peripheral vasodilation, whereas sympathetic activity increases in order to prevent a deeper reduction in blood pressure [22].

We have recently compared the hemodynamic changes induced by oral glucose and by a mixed meal including 50% of carbohydrates in healthy subjects. Oral glucose intake was followed by a slight increase (5 mmHg as a mean) of systolic blood pressure and a significant acceleration of heart rate, which were associated with a significant increase in plasma noradrenaline and with an enhancement of sympathovagal balance (towards a sympathetic predominance). On the contrary, the mixed meal was not followed by significant hemodynamic changes [23].

**Hemodynamic effects of oral glucose intake in particular situations**

The increase in systolic blood pressure induced by oral glucose intake might be higher in patients with arterial hypertension or glucose intolerance [24]. In normotensive diabetic patients, systolic blood pressure increases of 10 mmHg as a mean after oral glucose [23]. In hypertensive patients with type 2 diabetes the increase in blood pressure is even higher, up to above 25 mmHg and 12 mmHg as a mean, for systolic and diastolic values respectively. This increase is prevented by glutathione, an anti-oxidant agent, which suggests the role of oxidative stress in blood pressure increase after glucose [25].

Alterations in vagosympathetic activity may modify the hemodynamic changes induced by oral glucose or other single carbohydrates. We have previously suggested that a high vagal activity may be protective against hypertension associated with obesity [26]. Cardiac vagal activity is often depressed in overweight, hypertensive and diabetic subjects [27-29]. A high-carbohydrate isoenergetic meal has been shown to induce a significantly lower sympathetic activation than in healthy overweight, hypertensive and diabetic subjects; sympathetic activity was significantly lower in these subjects than in young subjects, in line with a lower sympathetic activity at baseline.

On the contrary, there were no significant changes in blood pressure after a mixed meal [23]. Thus, a depression in sympathetic activity might account for some non hypoglycemic postprandial dizziness episodes in elderly patients, in particular in those with diabetes, and the role of high glycemic index foods may be hypothesised.

**Prevention of the hemodynamic changes in the postprandial phase**

Not only oral glucose, but also fat, have been shown to induce oxidative stress as evidenced by an increase in serum nitrotyrosine and an impairment in peripheral endothelium function [33]. The most severe derangement is induced by a combined glucose and high-fat load. Even if there is no correlation between the increase in blood glucose or triglycerides and the rise in blood pressure, changes in endothelium function and sympathovagal activity induced by both components should be prevented.

There is no published data from controlled intervention trials showing that a reduction in single sugar intake or fat may prevent the increase in blood pressure. However some pharmacological intervention trials suggest that this could be efficient. In particular, the STOP-NIDDM trial has shown that in subjects with glucose intolerance, acarbose treatment reduces not only the occurrence of new diabetes cases, but also induces a 34% decrease in the incidence of hypertension and a 49% reduction of cardiovascular events as compared to placebo [34]. Acarbose treatment has also been shown to prevent acute endothelial function changes induced by saccharose in patients with impaired glucose tolerance together with a reduction of the increase in blood glucose after saccharose [35]. Acarbose slows also progression of carotid intima-media thickness in patients with impaired glucose tolerance [36]. In patients with type 2 diabetes the postprandial increase in prothrombin fragments 1 + 2 and D-dimer is also prevented by acarbose treatment [37]. A recent meta-analysis of seven controlled trials in patients with type 2 diabetes has shown a 35% reduction of cardiovascular events in patients treated by acarbose [38]. Repaglinide, a short-acting insulin secretagogues may be safe alternatives.
secretion enhancer, that acts mainly by reducing postprandial blood glucose, has been compared with glibenclamide in a 12-month controlled trial in patients with type 2 diabetes. The percentage of patients who reduced their carotid intima-media thickness more than 0.020 mm was three-times higher with repaglinide than with glibenclamide [39]. These data are consistent with a benefit in reducing postprandial blood glucose increase in a cardiovascular prevention perspective.

Other drugs have been tested to prevent endothelium dysfunction induced by oral glucose and/or fat load in normal subjects and in patients with type 2 diabetes. Both atorvastatin, an HMG-CoA reductase inhibitor, and irbesartan, a blocker of AT1 receptors of angiotensin-2, prevent oxidative stress and endothelium dysfunction induced by oral glucose or high-fat load, and the combined treatment by atorvastatin and irbesartan appeared to be the most effective [40]. Both treatments were active without significantly changing blood pressure and serum lipid parameters before meal tests, which suggests that they act mainly through their pleiotropic effects.

Conclusion

In conclusion, single sugar intake may induce an increase in blood pressure mediated by sympathetic activation and endothelium dysfunction. A high-fat load may similarly induce oxidative stress and endothelium dysfunction. Such effects might be more important in patients with vagal depression and sympathetic predominance and with an increase in oxidative stress at fasting. The pathogenic potential of the repeated intake of these nutrients on hypertension and surrogate markers of cardiovascular risk should be tested in long-term controlled trials. In elderly patients, in particular those with low sympathetic activity, single sugar intake could account for non hypoglycaemic postprandial dizziness.

References

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