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Effect of mental stress on cardiovascular function at rest and after ingestion of fructose or sucralose in healthy, white European males

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Aim: Ingestion of fructose and mental arithmetic can increase blood pressure (BP); the present study assessed the effect of fructose ingestion on cardiovascular (CV) response to mental stress. Effects were compared with sucralose used as a control.

Materials and methods: Ten healthy, white European males were studied twice. A Finometer recorded CV parameters, noninvasively, throughout the study period. After the 30-min baseline, a mental arithmetic task (MAT), a series of arithmetic questions displayed as PowerPoint slides, was presented. Subjects, while resting on a bed, answered 20 questions in 2 min; 15 min after MAT-1, volunteers consumed 500 mL of lemon-flavoured drink containing either fructose (0.75 g/kg body weight) or sucralose. Thirty minutes after drinking, MAT-2, using different questions, was administered; measurements continued for 30 min afterwards. The same protocol was repeated with new questions on a different day with the alternative drink, containing either fructose or sucralose.

Results: Fructose and sucralose increased BP and total peripheral resistance (TPR). MATs increased BP, heart rate, and cardiac index, whereas TPR decreased. CV responses to mental arithmetic were not affected by fructose or sucralose, except for an attenuated increase in SBP during MAT-2 after fructose.

Conclusion: Pressor effects of fructose (or sucralose) and MATs are not additive.

Key words: Fructose, sucralose, mental stress, cardiovascular function, Finometer

1. Introduction

It has been known that mental stress is associated with adverse cardiovascular (CV) events such as myocardial ischaemia, arrhythmias and left ventricular dysfunction (1,2). Such association increases the likelihood of subsequent fatal and nonfatal cardiac events (3). Mental stress can activate the sympathetic nervous system (SNS) and results in increased heart rate (HR) and blood pressure (BP), creating extra myocardial oxygen consumption and demand (4,5). An increase in the double product is directly related to mental stress (6); in patients with coronary artery disease, the maximum work load that can be managed by the myocardium is reduced and it is likely that this critical level will be exceeded by mental stress or mild exercise, which may precipitate angina (7).

Fructose has been in increasing use in human diet (8) and makes up about 8% of daily energy intake through food items (9). Use of refined sugars and that of fructose may be implicated in the present-day prevalence of obesity (10,11), which leads to adverse health effects such as hypertension, development of type-2 diabetes mellitus (12), and obstructive sleep apnoea (13). Recent studies demonstrated that acute consumption of fructose increased systolic BP (SBP) and diastolic BP (DBP) (14) and increased HR, cardiac output respiratory quotient, and oxygen consumption in humans (15). Sucralose is a synthetic sweetener that is 600 times sweeter than sucrose. It has been reported safe to consume and is well tolerated by humans (16).

The objective of the present study was to assess whether consumption of fructose acutely affected the CV system, and particularly the responses to mental stress, in healthy, white European males using sucralose as a control for fructose.

2. Materials and methods

Ten healthy, nonsmoking, white European males were recruited for this study of 8 months in duration, conducted at the Medical School of The University of Nottingham, Nottingham, UK. The study conformed to the principles set by the Declaration of Helsinki and was approved by The University of Nottingham's Medical School ethics

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committee. Subjects were aged 26 ± 2 years, weighed 69 ± 3 kg, and were 179 ± 2 cm tall. They were medically screened before study visits (2 visits). Before each visit, volunteers fasted for 3 h and avoided sugar-containing soft drinks, bakery products, fruit, fruit products, and strenuous exercise for 24 h.

The quantity of fructose added to the test drink was 0.75 g/kg body weight. Taste-matching of the fructose- and sucralose-containing drinks was done and it was calculated that 14 sucralose tablets taste-matched 52.5 g, i.e. the fructose used for 70 kg of body weight. This ratio was used to match all fructose doses. In previous studies, 60 g of fructose was used to determine effects of fructose on the human CV system (15). Personal experience also suggested that more than 70 g of fructose may induce gastrointestinal disturbance; hence, fructose dose was calculated according to the body weight of the volunteer. No volunteer complained of gastrointestinal upset after consuming the fructose. Sucralose dose was calculated to taste-match the sweetness of the fructose drink in preliminary studies performed by some staff of the School of Biomedical Sciences of The University of Nottingham.

Upon arrival for the experiment, volunteers voided their bladder and rested on a bed, semirecumbent, in a thermoregulated room, and the Finometer (FMS, Finapres Medical Systems BV, the Netherlands) arm cuff was attached to the left upper arm and a finger cuff was wrapped around the middle phalanx of the middle finger of the left hand. A data projector (In-Focus, LP-530, USA) displayed the mental stress test (MAT) as a PowerPoint presentation on the wall in front of the volunteer.

2.1. Protocol

Baseline recordings were made for 30 min; subsequently, a MAT was presented. During MAT-1, volunteers were asked to solve 20 simple arithmetic questions in 6 s each, i.e. in total time of 2 min. In pilot studies recruiting 6 volunteers, who were different from actual study volunteers, and by using different sets of questions for MAT-1 and MAT-2 in order to remove any chance of recognition/familiarisation of the MAT used in the main experiments, it was determined that the MAT had significant and reproducible CV effects while no drinks were offered during those experiments. Subjects said their answers loudly and the investigator communicated to them whether or not an answer was correct. During the task and for the subsequent 15 min, Finometer data collection continued. Volunteers were then offered 500 mL of lemon-flavoured, freshly prepared drink, the order of which was randomised. The drink was to be consumed over the course of 5 min and contained either fructose (Fruisana; Danisco Sweeteners OY, Finland) or sucralose (Splenda; McNeil Nutritionals Ltd., UK). Measurements after drinking continued for 30 min; thereafter, the second MAT (MAT-2) was administered with a different set of questions followed by post-MAT-2 recordings for 30 min. The same protocol was repeated on a separate day with the exception that the test drink and the set of MAT questions were different from the first experimental visit.

2.2. Data analysis

Collected data were averaged over 2-min intervals for the pre- and post-MAT period and at 20-s intervals for the MAT duration. Thus, mean values were calculated for the time periods of –2 to 0, 0 to 2, and 2 to 4 min before MAT, for 20-s intervals between 4 and 6 min (during the MAT), and for 6–8, 8–10, and 10–12 min after MAT. The period in which subjects consumed the drink was excluded from the data sheets. Statistical analysis was performed using Quade, Friedman, and Wilcoxon tests. Cardiac output, total peripheral resistance (TPR) and stroke volume (SV) were factored by the weight of the subject and statistical significance was set as $P < 0.05$.

3. Results

All baseline variables were similar prior to MAT-1, before the fructose- or sucralose-containing drinks were consumed (Table 1). Baseline HR tended to be higher before MAT-1 before the fructose drink (Table 1) as compared with after the fructose drink, before MAT-2 ($P = 0.059$) (Table 2).

Significantly higher baseline SBP, DBP, and mean arterial pressure (MAP) (9, 4, and 7 mmHg, respectively; $P < 0.05$) and TPR (0.096 units; $P < 0.001$) were noted after the fructose drink (i.e. before MAT-2) in comparison with pre-drink baseline values (before MAT-1). Post-sucralose drink baseline data showed SBP higher by 7 mmHg, DBP by 5 mmHg, MAP 8 by mmHg, and TPR by 0.118 units ($P < 0.01$), as compared with pre-drink sucralose baseline data. Post-drink (fructose and sucralose) baseline values were not, however, statistically different (Table 2).

3.1. Haemodynamic responses to mental stress

3.1.1. MAT-1 (before the drinks)

Significant elevations of SBP by 10% (13 mmHg) and of DBP and MAP by 12% (9 mmHg and 12 mmHg, respectively) above baseline were observed ($P < 0.001$) at around 1.5 min after the MAT began.

HR increased by 29% (20 beats), with a 30% change (2 L/min) above baseline in the cardiac index (CI) ($P < 0.001$). TPR went down by a maximum of 17% (–0.135 units; $P < 0.001$) at 40 s after the task began, gradually rising to 7% (+0.061 units) above the baseline in the recovery period ($P < 0.001$) (Figure 1).

As compared to MAT-1 (pre-fructose), pre-sucralose MAT resulted in similar but smaller elevations in SBP, which increased by 6% (8 mmHg), DBP by 7% (5 mmHg), and MAP by 9% (9 mmHg) ($P < 0.001$) at around 1.5 min after the MAT began. An increase of 7% in SV (7 mL; P <

Table 1. Pre-drink (fructose and sucralose) baseline data. No statistically significant difference in CV variables was noted. Values are mean ± SEM.

Variable	Pre-drink (fructose)		Pre-drink (sucralose)	
	Mean	SEM	Mean	SEM
SBP, mmHg	126	±2	131	±3
DBP, mmHg	72	±2	74	±2
MAP, mmHg	91	±2	94	±2
HR, beats/min	66	±3	66	±2
Cardiac output, L/min	7.0	±0.1	7.0	±0.1
TPR, resistance units	0.825	±0.03	0.848	±0.03
SV, mL	103	±3	105	±4

Table 2. Post-drink (fructose and sucralose) baseline data showing statistically significant changes in SBP, DBP, MAP, and TPR from the pre-fructose/sucralose (pre-MAT-1) baseline. Post-drink (fructose and sucralose) baseline values were not statistically different. Values are mean ± SEM.

Variable	Post-drink Mean	(fructose) SEM	P-value	Post-drink Mean	(sucralose) SEM	P-value
SBP, mmHg	135	±3	0.01	138	±3	0.007
DBP, mmHg	76	±1	0.046	79	±2	0.004
MAP, mmHg	98	±2	0.03	102	±2	0.004
HR, beats/min	63	±2	=0.059	63	±3	NS
Cardiac output, L/min	6.5	±0.1		6.5	±0.1	NS
TPR, resistance units	0.921	±0.04	0.00006	0.966	±0.05	0.004
SV, mL	104	±3		104	±4	NS

0.001) was noted at the same time that peak changes in BP occurred. HR increased by 19% (12 beats; $P < 0.05$) and a 23% increase (1.5 L/min; $P < 0.001$) in CI was recorded at 20 s after the task began. At the same time, TPR decreased maximally by 13% (–0.112 units; $P < 0.001$), recovering back to baseline in the post-MAT period (Figure 2).

3.1.2. MAT-2 (post-fructose drink)

During MAT-2, SBP, DBP, and MAP rose by 6% (8 mmHg), 7% (6 mmHg), and 8% (8 mmHg), respectively, from the baseline ($P < 0.001$) at around 1.5 min after the MAT began. In the MAT's first 20 s, HR and CI increased by 31%, i.e. a rise of 20 beats in HR and 2 L/min in CI ($P < 0.001$). TPR remained below baseline during the MAT, with a 20% drop (–0.175 units) noted in the first 20 s ($P < 0.001$) (Figure 1).

3.2. Comparison of MAT-1 (pre-fructose) with MAT-2 (post-fructose)

The Wilcoxon signed-rank test was used to compare responses to MAT-1 and MAT-2. There were greater BP responses to MAT-1 compared to MAT-2 ($P < 0.05$) (Figure 1).

3.2.1. MAT-2 (post-sucralose drink)

One min after MAT-2 began, SBP rose by 4% (5 mmHg; $P < 0.05$) and DBP and MAP increased by 6% (5 and 6 mmHg, respectively) from baseline ($P < 0.001$). HR and CI increased in the first 20 s of the MAT by 26%, i.e. 16 beats and 1.6 L ($P < 0.001$). A simultaneous 19% decrease (–0.187 units; $P < 0.001$) in TPR was noted; TPR recovered back to baseline as the MAT finished (Figure 2).

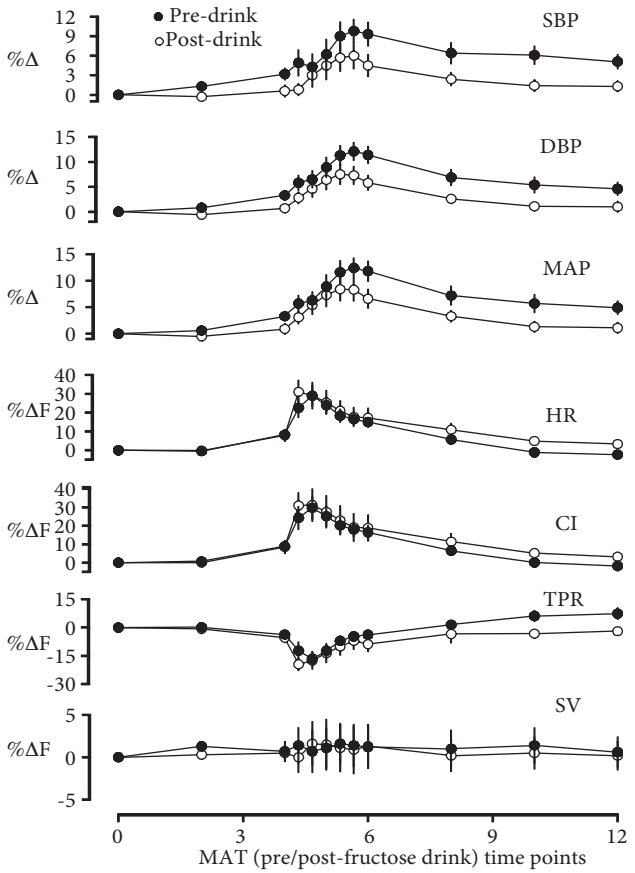

Figure 1. Comparison between CV responses to MAT-1 and MAT-2. Higher BP responses with MAT-1 are evident. Other CV variables show no difference between responses. Data are mean ± SEM. %Δ = Percentage change; %ΔF = Percentage change factored.

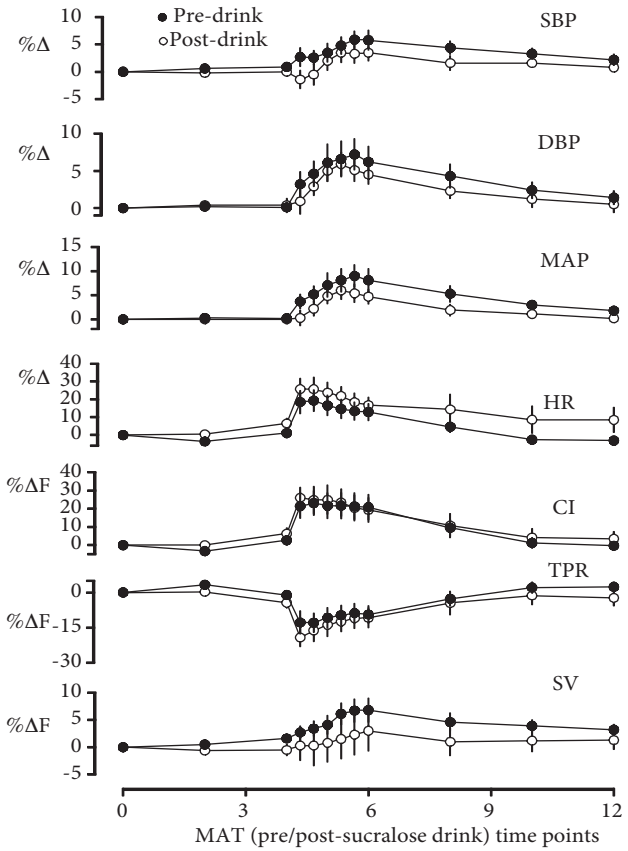

Figure 2. Difference in SBP before and after sucralose-containing drink was consumed. All other CV parameters are similar. Data are mean ± SEM.

3.2.2. Comparison of MAT-1 (pre-sucralose) with MAT-2 (post-sucralose)

The Wilcoxon signed-rank test was used to compare MAT-1 and MAT-2; significantly higher SBP values ($P < 0.05$) were noted during MAT-1 (pre-sucralose) (Figure 2).

3.3. Comparison between the effects of the 2 drinks on the mental arithmetic responses

Using the Wilcoxon signed-rank test, responses to the MAT before and after fructose or sucralose drink consumption were compared; no statistically significant difference was noted between the 2 experiments.

4. Discussion

The present study determined acute effects of mental arithmetic-induced mental stress on the CV system with and without fructose ingestion in healthy volunteers. CV parameters were recorded beat-to-beat, noninvasively, using a Finometer. It was determined that MAT in the baseline (pre-drink) condition significantly raised BP, HR, and CI, while TPR decreased. A significant increase in SV was only seen before the sucralose drink. These results are consistent with the findings that MATs result in increase in BP and that the reaction is mainly mediated through an increase in cardiac output (17).

Consumption of fructose and sucralose significantly increased BP and TPR compared to pre-drink baseline values. Similar but smaller CV responses were observed to MAT-2 than the responses to MAT-1. Although this was not significant in the case of sucralose, the BP responses to MAT-2 after fructose were significantly lower than those noted for MAT-1 before fructose. There was a trend for greater decreases in TPR after MAT-2 as compared to during MAT-1 (by 3% after fructose and 6% after sucralose), but these were nonsignificant.

Acute episodes of mental stress activates the SNS, leading to catecholamine release (18,19) and particularly adrenaline, which reaches its peak serum levels at 1 min versus noradrenaline at 5 min (20). In the present study,

mental stress increased BP, HR, and CI and decreased TPR. These responses may well have been due to direct effects of catecholamines and it is likely that adrenaline action on the β_1-adrenoceptor increased CI, consequently increasing BP. Decrease in TPR occurred simultaneously and thus is unlikely to have been due to baroreflex response, although if this occurred very rapidly it may not have been detected. TPR then returned to baseline during the second half of the MAT, whereas CI remained above baseline (but below peak values) and BP continued to rise. Such responses reflect continued SNS activation due to continuing rise in plasma noradrenaline levels, as previously illustrated by Becker et al. (20).

Evidence suggests that a decrease in DBP and MAP, and vasodilatation in the calf vascular system and a trend for a vasoconstrictor effect on the hand vasculature, can occur at both intermediate and higher plasma adrenaline concentrations, but a rise in SBP can only occur with higher plasma adrenaline concentrations (21). Although no blood tests were performed, as invasiveness may have resulted in further stimulation of the SNS distorting the results, these findings support the view that adrenaline release in response to mental stress may have produced both vasodilatation and an increase in CI. Vasodilator response to mental stress was confirmed by Harris et al., who reported an increase in brachial arterial diameter with mental stress as compared to that without mental stress (4). In the present study also, vasodilatation is reflected by decrease in TPR with mental stress, facilitating oxygen delivery to tissues.

When effects of fructose consumption on the baseline state (before MAT-2 commenced) were analysed, it was found that there was a significant rise in SBP, MAP, DBP, and TPR; sucralose had similar effects. One concern was that the initial MAT occurred between the 2 baselines and it was unclear whether the pre-MAT-2 baseline increases were the result of a prolonged effect of mental arithmetic or fructose ingestion. To clarify this, baseline values before each bout of mental stress in the pilot study were looked at. Those values were found to have much smaller differences before and after MAT-1 than those that were seen when fructose was consumed after MAT-1. This is illustrated by the observation that change in TPR between baseline measurements was significantly greater after fructose ($P < 0.05$) than in the pilot when no drink was consumed. Thus, it seems likely that increases in CV parameters before MAT-2 may have been due to fructose consumption. However, similar results after sucralose suggest that it might be the sweet taste rather than any metabolic effects that leads to such increases in BP and TPR. With the fructose and sucralose drinks, elevated TPR was noted before MAT-2 and it then fell as the task commenced, suggesting that the CV responses to mental arithmetic may not have been affected by fructose or sucralose consumption.

A significant increase in SV with the pre-sucralose MAT may have been due to a baroreflex influence on HR, as it is evident from Figure 2 that with the increase in BP there was a corresponding decrease in HR, providing extended ventricular relaxation time and thus increasing SV. However, pre-sucralose change in SV was not different from the pre-fructose values, indicating that increase in SV (pre-sucralose MAT) could be a minor response that was significant within the day but not between days.

The present study had certain limitations, such as the small sample size and lack of information on plasma catecholamine levels; more studies with larger numbers of subjects and evaluation of stress hormone levels may be designed to get more insight into this area. Furthermore, a water control is necessary before conclusions can be drawn about potential effects of sucralose.

It is concluded that a compensatory decrease in TPR is likely to occur with mental stress in healthy humans and that fructose ingestion may result in high TPR. There seems to be no cumulative effect of consumption of fructose- or sucralose-containing drinks with mental stress as the amount of change after the drink was consumed was smaller as compared with that when the drink was not consumed. Higher baseline values after fructose and sucralose consumption might have obscured the actual magnitude of change in CV variables that would have otherwise been similar or higher if not taken from an elevated baseline value.

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