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Effect of sucrose consumption on serum insulin, serum cortisol and insulin sensitivity in migraine: Evidence of sex differences

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HIGHLIGHTS

- Level of insulin after eating sugar is not the same in male and female migraineurs.
- Level of insulin after eating sugar is higher in female migraineurs.
- Effect of sugar on insulin sensitivity in male and female migraineurs is different.
- Sugar-induced insulin resistance develops after 120 min in female migraineurs.

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ABSTRACT

The aim of this study was to compare the effect of sucrose on biomarkers of energy metabolism and utilization in migrainous men and women. A total of 20 participants (7 = Migraine (female), 5 = Migraine (male), 8 = Non-migraine control) submitted to an oral sucrose tolerance test (OSTT), which required them to fast for 15 h overnight and then ingest 75 g sucrose dissolved in 175 g water at 9 AM the next morning. Blood sampling for the assessment of serum insulin, serum cortisol and plasma glucose was conducted upon arrival at 0900 h and then at regular 15-min intervals across a 150-min period. Comparison of insulin sensitivity indexes that rely on fasting glucose and insulin data failed to find evidence of insulin resistance in migraineurs or controls. Prior to sucrose consumption the level of fasting serum cortisol at 0-min on average was significantly higher in migraineurs. However, no significant group differences in the level of fasting serum insulin and plasma glucose at 0-min were noted. Following sucrose consumption: the level of serum insulin was significantly higher in female migraineurs; the level of serum cortisol was significantly higher in male migraineurs; glucose/insulin (G/I) ratio was significantly higher in male migraineurs at 135-min and 150-min; insulin/cortisol (I/C) ratio was significantly different with the I/C ratio lower in male migraineurs and higher in female migraineurs; area under the curve (AUC) insulin was significantly different across groups with AUC insulin lower in male migraineurs and higher in female migraineurs; and AUC cortisol was significantly higher in male migraineurs. It was concluded that the effect of sucrose on biomarkers of energy metabolism and utilization in male and female migraineurs is not the same. Therefore, the factors underlying migraine pathogenesis in men and women may also be different.

1. Introduction

Migraine is a neurovascular disorder that is characterized by recurring headache of unilateral onset, photophobia, phonophobia and autonomic disturbances [19,22]. A systematic review of population-based studies reporting migraine prevalence found that the incidence of chronic migraine was estimated to range from 0 to 5.1% [34]. Moreover, sex differences have been reported with women up to four times more likely than men to be affected [31].

The association between migraine and vascular disorders (e.g. coronary heart disease, stroke) and vascular diseases (e.g. hypertension, ischemic brain injury) is well accepted [49]. However, in the last few years it has become apparent that a relationship between migraine and insulin resistance may exist [38]. Clinical data has confirmed that insulin resistance is a risk factor for hypertension [30], stroke [25] and cardiovascular disease [13]. Thus, insulin resistance could be the key factor linking migraine to vascular conditions [41].

Migraine patients often report migraine symptoms after consuming food containing refined sugar [23]. Refined sugar is a known migraine trigger [39] and eliminating sucrose from the diet can promote a 75% reduction in migraine symptoms [11,27]. In the past, it has been shown that the consumption of sucrose can increase the risk of insulin

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resistance in humans [44] and animals [6,42]. However, whether ingesting sucrose promotes insulin resistance in migraineurs is unknown.

More recently it has been suggested that males may be at greater risk of developing cardiovascular disease due to having an increased vulnerability to insulin resistance [20]. Improved insulin sensitivity has been observed in conjunction with higher levels of the female sex hormone estrogen [12] and lower levels of the male sex hormone testosterone [35]. However, it is important to note that the level of estrogen fluctuates across the female menstrual cycle with estrogen lowest post-ovulation during the luteal phase. Women commonly report developing migraine symptoms during the luteal phase of their menstrual cycle [9]. Thus, women are more likely to develop migraine symptoms during periods when their risk of developing insulin resistance is also increased [14].

The consumption of sugar sweetened beverages can significantly elevate the level of estrogen in premenopausal women [43], which in turn can act on pancreatic beta cells and promote insulin synthesis and release [1]. Similarly, consuming a sugar sweetened beverage can significantly elevate serum insulin concentration in female migraineurs [28]. However, whether a similar sucrose-induced alteration in serum insulin also occurs in male migraineurs is unknown.

There is increasing evidence that a relationship may exist between migraine and insulin resistance [38]. Moreover, a relationship between sex hormones and insulin resistance [12,35] and insulin synthesis/release [1] has also been reported. Furthermore, if we consider that consuming sucrose can significantly increase estrogen [43] it would not be unreasonable to suspect that the effect of sucrose on insulin synthesis/release and insulin sensitivity in male and female migraineurs males could be different. However, while we know that ingesting sucrose can significantly elevate serum insulin in female migraineurs [28] it is unclear what effect (if any) sucrose has on the level of serum insulin (over time) in male migraineurs or insulin sensitivity in both male and female migraineurs. Thus, the aim of the present study is to address the gap in the migraine literature by comparing the effect of a sucrose load on serum insulin concentration and insulin sensitivity in normotensive male and female migraineurs.

2. Materials and methods

2.1. Participants

A total of 21 participants aged between 38 and 55 years were recruited for the migraine and non-migraine group via a general advertisement placed in local and community newspapers. The migraine group consisted of 8 women (age range = 22–49 years, M = 41.1 years, SD = 9.1 years) and 5 men (age range = 33–55 years, M = 45 years, SD = 7.8 years) who satisfied the International Headache Society (IHS) migraine criteria [21]. The non-migraine group consisted of 8 women (age range = 42–54 years, M = 47.1 years, SD = 4.1 years) who did not satisfy the IHS classification and diagnostic criteria for headache disorders [22].

Participants were excluded if they: (1) had any history of psychiatric disorder, neurological disease, or any major physical complaint including hyper/hypothyroidism and diabetes; (2) regularly took prescription medication; (3) consumed any substance containing nicotine or alcohol within 48 h; (4) were using oral contraceptives or undertaking hormone replacement therapy; or (5) were post-menopausal.

The participants in this study were white Caucasians of European or English background. The weight of participants was within the medically recommended range for age and height (BMI < 27.5 kg/m^2). All were reportedly non-smokers and social consumers of alcohol. Subject participation was obtained by informed consent and no financial or other incentives were provided to any participant in return for participation in this study. The procedures employed in this study were consistent with ethical guidelines for human research set by the National Health and Medical Research Council of Australia (2007) [54].

2.2. Equipment and assays

Serum insulin was assessed by Cobas Elecsys 2010® immunoassay (Roche Diagnostics, Indianapolis, IN, USA). The sensitivity of the insulin assay is .20 μU/mL (lower detection limit) and the intraassay coefficient of variation (CV) of the insulin assay is 1.9% at 44.2 μU/mL and 1.9% at 145 μU/mL. Values in the 5th–95th percentile range for healthy fasted individuals were 2.6–24.9 μU/mL for serum insulin. Serum cortisol was also assessed by Cobas Elecsys 2010® immunoassay (Roche Diagnostics, Indianapolis, IN, USA). The sensitivity of the cortisol assay is 0.5 nmol/L (lower detection limit) and the intraassay CV of the cortisol assay was 3.2% at 202 nmol/L, 3.1% at 377 nmol/L, and 2.2% at 546 nmol/L. Values in the 5th–95th percentile range for healthy fasted individuals were 171–536 nmol/L for serum cortisol. Staff at Analytic Reference Laboratories (St Kilda Road, Melbourne, VIC), who were blind to the experimental procedure, performed all biochemical analyses.

A total of 75 g refined sugar in the form of commercially available white sucrose, dissolved in 175 mL water, was used as the carbohydrate load. Plasma glucose was assessed using a Caresens® (i-SENS Inc, Korea) plasma glucose monitoring system. Semi-quantitative urinalysis was performed with Labstix™ (Bayer Australia Limited) to measure ketones (sensitivity was 0.5–1.0 mmol/L acetoacetic acid).

2.3. Experimental procedure

All participants were required to undergo a structured interview prior to participation in the study. During the structured interview the interviewer (a registered psychologist) asked participants to respond to questions relating to: demographic factors (age, gender, marital and cohabitation status, level of education, and occupation); lifestyle factors (diet, exercise, alcohol and tobacco usage); headache history (type, duration, medication, use of alternative therapies, hospitalization); medical history (individual and relevant family aspects, menstrual disorders, use of oral contraceptives, mood disorders, psychosis); any physical or emotional trauma. At the completion of the interview the headache status of all participants was assessed against the IHS primary headache criteria [21].

Blood glucose level can vary across the menstrual cycle [4]. Moreover, insulin resistance has been linked to the sex hormone estrogen [14]. Therefore, given that the level of sex hormones can vary across the menstrual cycle a total of three oral sucrose tolerance test (OSTT) sessions were conducted. There was a one week interval between OSTT sessions and female participants were allocated to the testing session as near as possible to the mid-point of their menstrual cycle. Men on the other hand were assigned to one of the three testing sessions based purely on convenience factors.

All participants were asked to maintain a minimum carbohydrate intake of 150 g/day for three days prior to their scheduled testing session. On the day prior to testing strenuous exercise was not permitted and all participants were required to maintain a 15 h fast commencing at 1800 h Eastern Standard Time (EST). Testing was scheduled the following morning at 0900 h EST. Upon arrival a catheter was fitted to the left forearm of each participant in order to facilitate repeated blood sampling and minimize stress associated with the blood sampling procedure. At 0900 h participants were asked to provide a 50 mL urine sample for urinalysis prior to having 10 mL of blood drawn from their left forearm for assessment of serum insulin, serum cortisol and plasma glucose. Following the blood taking procedure participants immediately ingested 75 g sucrose, which had been dissolved in 175 mL water. Sucrose ingestion was monitored to ensure that the rate of consumption was the same for all participants. Further blood sampling for the assessment of serum insulin, serum cortisol and plasma glucose was performed at regular 15-min intervals. Physical activity was restricted