นิพนธ์ต้นฉบับ • Original Article

การบริโภคน้ำตาลมากเปลี่ยนแปลงการทำงานของประสาทไตให้มีลักษณะที่จำเพาะต่อการคัดหลั่งเรนินมากขึ้นในหนูที่สลบ

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High Sugar Intake Alters a Pattern of Renal Nerve Activity Specifically to Increase Renin Release in Anesthetized Rats

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หลักการและวัตถุประสงค์ : การบริโภคน้ำตาลมากเปลี่ยนแปลงการทำงานของไตก่อนทำให้ความดันเลือดสูงขึ้น และมีภาวะต้านทานอินซูลิน โดยเพิ่มการทำงานของระบบเรนินร่วมแองจิโอเทนซิน ส่วนการคัดหลั่งเรนินขึ้นกับทั้งการทำงาน และลักษณะการตอบสนองของประสาทซิมพาเทติกที่มาเลี้ยงไต การศึกษาครั้งนี้ต้องการทดสอบสมมุติฐานที่ว่าอาหารที่มีน้ำตาลมากเปลี่ยนแปลงลักษณะการทำงานของประสาทไตในช่วงความถี่ของความแปรปรวนที่เกี่ยวกับการคัดหลั่งเรนินในหนูเพศผู้วัยโตเต็มที่

วิธีการศึกษา : หนูเพศผู้พันธุ์ Sprague-Dawley ถูกเลี้ยงด้วยอาหารหนูและน้ำประปาที่ผสมด้วยกลูโคสร้อยละ 5 (กลุ่มกลูโคส) หรือน้ำประปาอย่างเดียว (กลุ่มควบคุม) ตั้งแต่หลังหย่านมจนสิ้นสุดการทดลอง เมื่อหนูอายุ 7-8 สัปดาห์ ทำการวัดสารเคมีในเลือด ความดันเลือดแดง อัตราการเต้นของหัวใจ และการทำงานของประสาทซิมเทติกที่มาเลี้ยงไตในภาวะที่หนูถูกวางยาสลบ

ผลการศึกษา : น้ำหนักตัว ความดันเลือดแดงเฉลี่ย อัตราการเต้นของหัวใจ พลาสมาโซเดียม พลาสมาโปแตสเซียม พลาสมาไบคาร์บอเนต พลาสมาคลอไรด์ พลาสมาครีเอตินีน ยูเรียไนโตรเจนในเลือด และอัตราการเกิดสัญญาณประสาทไตไม่มีความแตกต่างกันในระหว่างกลุ่ม เมื่อวิเคราะห์เพาเวอร์สเป็คตรัมลักษณะการทำงานของประสาทไต โดยใช้ fast Fourier transformation พบว่า การบริโภคน้ำตาลมากเพิ่ม power spectral density ในช่วงความถี่ 0.25-0.75 เฮิร์ตซ์ (สัมพันธ์กับการคัดหลั่งเรนิน) เมื่อเทียบกับกลุ่มควบคุม

Background and Objective: High sugar intake can alter renal excretory function before inducing hypertension and insulin resistance via an increase in renin-angiotensin system activity. Renal renin release is dependent on renal sympathetic nerve activity and its pattern of response. This study tests the hypothesis that a high sugar diet after weaning alters a pattern of renal nerve activity variability at the frequency component related to renin release in adult male rats.

Methods: Male Sprague-Dawley rats were fed normal rat chow and tap water containing 5% glucose (glucose group) or water alone (control group) after weaning until end of the experiment. At 7-8 weeks of age, blood chemistry, arterial pressure, heart rate, and renal sympathetic nerve activity were measured in anesthetized rats.

Results: Body weight, mean arterial pressure, heart rate, plasma sodium, plasma potassium, plasma bicarbonate, plasma chloride, plasma creatinine, blood urea nitrogen, and renal nerve firing rate were not significantly different between the two groups. Power spectral analysis of renal nerve activity pattern by using fast Fourier transformation indicated that compared to control, high sugar intake increased the power spectral density between 0.25 to 0.75 Hz (related to renin

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โดยไม่มีผลกระทบต่อช่วงความถี่ที่มากกว่า 0.75 เฮิร์ตซ์ (1.0-2.5 เฮิร์ตซ์ สัมพันธ์กับการขับทิ้งโซเดียม และ 2.0-5.0 เฮิร์ตซ์สัมพันธ์กับการไหลของเลือดมาเลี้ยงไต)

สรุป : ข้อมูลเหล่านี้ชี้ให้เห็นว่า อาหารที่มีน้ำตาลมาก เปลี่ยนแปลงการทำงานของประสาทไต ในลักษณะที่จำเพาะต่อการเพิ่มการทำงานของระบบเรนินร่วมแองจิโอเทนซิน

คำสำคัญ ความดันเลือดแดง น้ำตาลมาก ประสาทไต ระบบเรนินร่วมแองจิโอเทนซิน ประสาทซิมพาเทติก

release), while that above 0.75 Hz (related to sodium excretion (1.0-2.5 Hz) and renal blood flow (2.0-5.0 Hz)) were not affected.

Conclusion: These data indicate that a high sugar diet after weaning alters a pattern of renal sympathetic nerve activity specifically to increase renin-angiotensin system activity.

Key words: blood pressure, high sugar, renal nerve, renin-angiotensin system, sympathetic nerve

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Introduction

Sympathetic nervous system overactivity underlies many disorders particularly hypertension, coronary vascular disease, and renal dysfunction[1,2]. In the kidney, an increase in sympathetic nerve activity increases renin secretion, decreases sodium excretion, and decreases renal blood flow. However, the degrees of these renal parameter responses to the sympathetic nerve activity are different. Several lines of evidence report that its pattern rather than firing rate specifically affects renal function; i.e., different patterns of renal nerve activity alter different renal parameters despite similar renal nerve firing rate[3]. Power spectral analysis of renal sympathetic nerve activity indicates that frequency components of power spectrum between 0.5-1.5 Hz stand for renin release, 1.0-2.5 Hz for sodium excretion, and 2.0-5.0 Hz for renal blood flow.

Several studies report that high sugar diets particularly fructose and glucose increase sympathetic nerve activity and renin-angiotensin system[4]. Male rats treated with 5% glucose in drinking water after weaning for four weeks display renal dysfunction without glucose intolerance and hypertension and these adverse effects are abolished by short-term inhibition of renin-angiotensin system[5]. Although local and systemic renin-angiotensin system might contribute to these adverse effects of high sugar, increased renal renin release by renal sympathetic nerve overactivity is proposed. Lines of evidence indicate that fructose-induced hypertension can be abolished by inhibition of either renin-angiotensin system or sympathetic nerve activity, as well as renal denervation[4]. However, high glucose intake for four weeks after weaning does not affect resting autonomic nerve activity and baroreflex-mediated renal nerve activity in male and female rats[6-8]. In another example, perinatal taurine excess or deficit does not alter renal nerve firing rate but alters renal sympathetic nerve activity patterns in adult rats[9]. Whether the pattern of renal nerve activity is modified by a high sugar diet has not yet been reported. The present study tests the hypothesis that high sugar intake after weaning alters a pattern of renal nerve activity at the frequency components related to renin release in adult male rats.

Materials and Methods

Sprague-Dawley rats were obtained from the National Laboratory Animal Center, Mahidol University, Nakhon Pathom, Thailand. They were then treated at the animal unit of Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. Female Sprague-Dawley rats were fed normal rat chow and tap water from conception to weaning. Male offspring were fed with the normal rat chow with either 5% glucose in tap water (glucose group) or tap water alone (control group) throughout the experiment. All experimental procedures were approved by the Khon Kaen University Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health guidelines.

At 7-8 weeks of age, the male rats were anesthetized with Nembutal (50 mg/kg, i.p.) and implanted with femoral arterial and venous catheters. Three days later, rats were anesthetized with Nembutal, tracheostomized, and continuously recorded arterial pressure, respectively. Renal sympathetic nerve was then exposed and continuously recorded by using stainless steel electrodes (12 MΩ, 0.01 Taper, Model 5727; A-M System, Sequim, WA, USA) connected to DAM-80 amplifier (DAM 80; World Precision Instruments, Sarasota, FL, USA) and BIOPAC Systems (BIOPAC Systems, Goleta, CA, USA), respectively. A multiunit recording of renal nerve activity was conducted only on nerve units that responded to changes in arterial pressure following sodium nitroprusside or phenylephrine infusion. Body temperature was servo-control at 37 ± 0.5°C by a rectal probe connected to a temperature regulator controlling an overhead heating lamp. At the end of experiment, blood volumes (about 1.0 ml) were collected from abdominal aortas for analysis of non-fasting plasma sodium, plasma potassium, plasma bicarbonate, plasma chloride, plasma creatinine, and blood urea nitrogen. Finally, all animals were terminated by a high dose of anesthesia.

Mean arterial pressure, heart rate, and renal nerve activity were analyzed by Acknowledge software (BIOPAC Systems, Goleta, CA, USA). Power spectral density of renal nerve activity was generated by using fast Fourier transformation[9]. Data are expressed as mean ± SEM. Comparisons between groups were performed using Wilcoxon signed-rank test (Statmost version 3.5, Dataxiom, USA) with a significant criterion of p-value less than 0.05.

Table 1 Basic characteristics of the animals

Parameters	Control (n = 8)	Glucose (n = 4)
Body weight (g)	240 ± 4	257 ± 5
Mean arterial pressure (mm Hg)	92.3 ± 2.0	101.3 ± 0.7
Heart rate (bpm)	370 ± 15	340 ± 36
Plasma sodium (mEq/l)	138.1 ± 1.3	144.8 ± 1.5
Plasma potassium (mEq/l)	4.7 ± 0.4	3.9 ± 0.2
Plasma bicarbonate (mEq/l)	22.4 ± 2.2	18.7 ± 1.3
Plasma chloride (mEq/l)	102.6 ± 1.4	102.5 ± 1.1
Plasma creatinine (mg/dl)	0.20 ± 0.03	0.18 ± 0.04
Blood urea nitrogen (mg/dl)	27.0 ± 2.2	22.6 ± 1.4
Renal nerve firing rate (spikes/sec)	99.4 ± 1.4	100.2 ± 0.6

Data are mean ± SEM. No significant differences between groups were observed (Wilcoxon signed-rank test).

Results

At 7-8 weeks of age, body weight, mean arterial pressure, heart rate, plasma sodium, plasma potassium, plasma bicarbonate, plasma chloride, plasma creatinine, blood urea nitrogen, and renal nerve firing rate were not significantly different between the two groups (Table 1). Compared to control, high sugar intake increased the power spectral density between 0.25 to 0.75 Hz (Figure 1). However, the high sugar intake did not affect the power spectral density of renal nerve activity at the frequencies above 0.75 Hz. In addition, the patterns of renal nerve activity at the frequency below 0.1 Hz differed between the two groups.

Discussion

High sugar intake from weaning until 4 weeks decreases water and sodium excretion due to an increase in renal tubular water and sodium reabsorption despite a sharp rise in glomerular filtration in adult male rats[5]. Further, renal vascular resistance and blood flow are not affected by a high sugar diet. These adverse effects of high sugar intake are abolished by a short-term treatment of angiotensin converting enzyme inhibitor captopril, suggesting the major role of renin-angiotensin system overactivity. However, this high sugar intake does not alter sympathetic and parasympathetic nerve activity estimated by arterial pressure variability in both male and female rats[6;10]. In addition, the baroreflex-mediated renal nerve activity is not altered by a high sugar diet in male and is decreased in female rats. Lines of evidence indicate that renal nerve activity pattern rather than firing rate specifically affects renal renin release, sodium excretion, and renal blood flow[3]. The present data is the first to indicate that the renal sympathetic nerve activity pattern is altered by a high sugar diet specifically to increase renin release.

Systemic renin-angiotensin system is mainly activated by renin release from juxtaglomerular cells. Low renal perfusion pressure and increased renal sympathetic nerve activity are the main factors that increase renal renin secretion. Renal innervation is quite complex. Although some nerve axons of renal sympathetic nerve may innervate several structures of the kidney, a group of nerve axons or nerve unit to juxtaglomerular cells are mostly separated from that to renal tubule or renal vasculature[3]. Thus, the central sympathetic pathway can specifically regulate the renal function. Hypotension, hypercapnia, hypoxia, and pain can stimulate renal sympathetic nerve activity but at different nerve units[11]. These different responses cannot easily be explored by a multiunit recording of renal nerve activity, but can be explained by power spectral analysis of renal nerve activity. Both power spectral density and pattern at different frequency components can explain specifically the action of renal sympathetic nerve on renal function. The present study suggest that high sugar intake may affect some brain areas that specifically regulate the sympathetic outflow to the juxtaglomerular cells and increases renin secretion. However, these may not be due to hyperglycemia, hyperinsulinemia, and insulin resistance since they are not observed in rats treated with a high sugar diet for four weeks[6;7].

The similar pattern of renal nerve activity spectrum at frequency components above 2.0 Hz supports previous experiments indicating that a high sugar diet did not affect renal blood flow[5;12]. Further, the similar pattern between 1.0-2.5 Hz suggests that the decreased tubular water and sodium excretion following the high sugar intake[5] may not be due to increased renal sympathetic nerve activity to the renal tubule. This increment is likely due to an increase in renin-angiotensin system since they are abolished by treating the animals with an angiotensin converting enzyme inhibitor captopril[5].

In the present study, high sugar intake did not affect arterial pressure and plasma electrolytes, suggesting that baroreceptor and probably chemoreceptor-mediated renal sympathetic responses is unlikely. Normal creatinine and blood urea nitrogen, as well as plasma

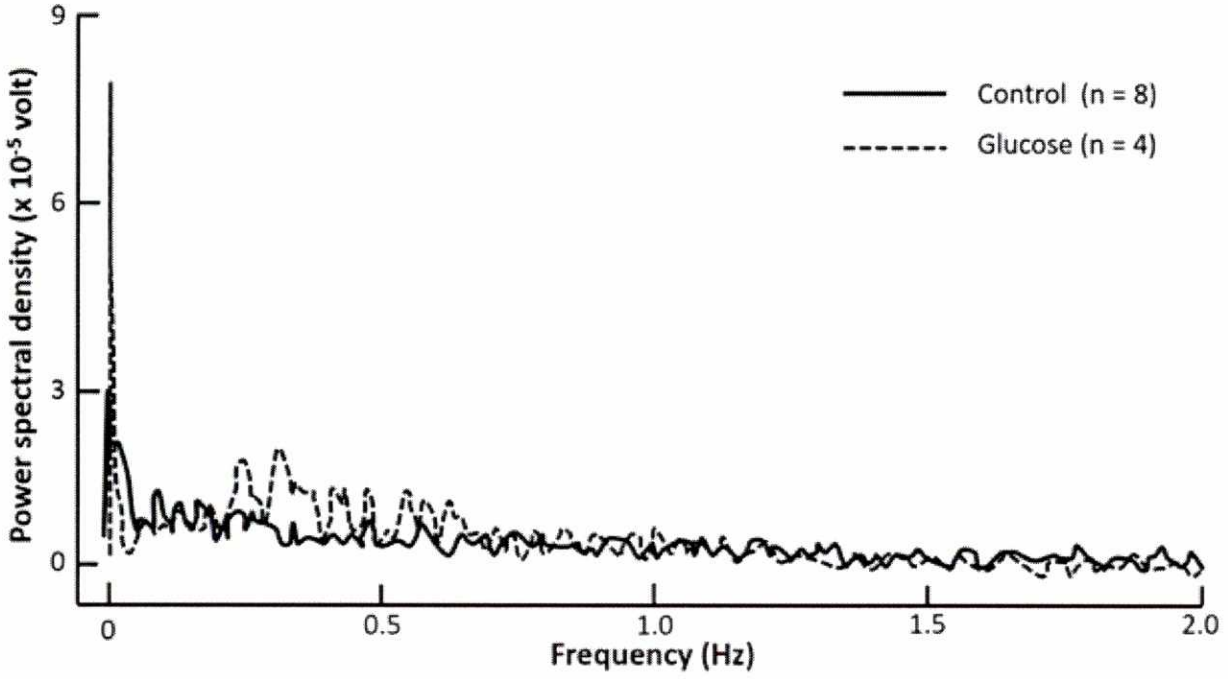

Figure 1 Patterns of renal nerve activity variability in control (thick line) and glucose (dash line) groups. Each graph is averaged from 8 (control) and 4 rats (glucose), respectively.

electrolytes indicate no severe renal dysfunction after a high sugar diet. These changes are similar to our previous reports[5;6].

Renal nerves are composed of afferent and efferent fibers. While the afferent fibers involve renal ischemic and injury response, the efferent fibers are sympathetic nerve fibers playing three different functions in the kidney as mentioned earlier. Although the firing rate of renal nerve activity may not increase in some forms of hypertension, renal denervation can prevent or improve hypertension in animals and humans[13;14]. These may be due to the fact that both firing rates and patterns of renal nerve activity contribute importantly to renal function. This study supports the notation that the pattern rather than the firing rate of renal nerve activity specifically affects renin secretion, sodium excretion, and renal blood flow.

Conclusion

High sugar intake can alter renal function without insulin resistance and hypertension by increasing renin-angiotensin system activity. This adverse effect of a high sugar diet has been hypothesized to be a consequence of heightened sympathetic nerve activity to the kidney. However, a multiunit recording of renal nerve firing rate mostly fails to support this hypothesis. These may be due to the fact that different renal structures are innervated by different renal sympathetic nerve units. The present data is the first to indicate that the renal sympathetic nerve activity pattern is altered by a high sugar diet specifically to increase renin release without direct effects on sodium excretion and renal blood flow. Thus, both firing rates and patterns of renal nerve activity should be measured in order to interpret the renal effect of sympathetic nerve activity.

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