Basal and Postprandial Serum Levels of Gastrin in Normotensive and Hypertensive Adults

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Abstract

Gastrin is a peptide hormone, which acts not only to regulate gastric acid secretion, but also to exert physiological actions such as the regulation of sodium balance. From a case (n = 95)-control (n = 82) study in Fuyang People’s Hospital, Anhui Province, China, we found that the fasting serum gastrin levels are similar in normotensive and hypertensive adults but increased to higher levels in the latter group than in the former group after a mixed meal. We suggest that gastrin is involved in the regulation of blood pressure, possibly via the regulation of sodium and water metabolism and/or renin-angiotensin-aldosterone system. However, the mechanism remains to be determined.

Keywords: aldosterone, angiotensin II, gastrin, hypertension

INTRODUCTION

Gastrin, a peptide hormone secreted primarily by G-cells in the stomach and duodenum, in response to food intake, is also released into the circulation. It is the principal mediator of meal-induced gastric phase of acid secretion, acting via paracrine stimulation of histamine release from gastric Enterochromaffin-like (ECL) cells (1–3). Gastrin acts on its receptor, the cholecystokinin B receptor (CCKBR), not only to regulate gastric acid secretion and oxyntic gland proliferation, but also to exert physiological actions outside of the gastric mucosa, including the colon, pancreas, small intestine, liver, esophagus, kidney, ovary, and brain (4).

Hypertension, a well-established risk factor for the development of stroke, coronary artery disease, peripheral artery disease, heart failure, and kidney disease, is a multifactorial disorder resulting from interactions between environmental and genetic factors (5). Gastrin negatively regulates renal sodium transport which is important in the normal regulation of blood pressure (BP) (6). Gastrin is important in the regulation of sodium balance and BP, as mice lacking gastrin have increased BP (unpublished data). Genome-wide association studies show that the chromosomal loci of CCKBR and gastrin are linked to hypertension (7–9). We hypothesized that gastrin may be involved in the regulation of BP.

METHODS

Subject Selection

This case–control study was performed in Fuyang People’s Hospital, Anhui Province, China. Subjects were selected from the employees of the hospital and divided into hypertensive and control groups. Hypertension was defined using The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) criteria as follows: average of three measurements of systolic blood pressure (SBP) ≥ 140 mm Hg or average of three measurements of diastolic blood pressure (DBP) ≥ 90 mm Hg on two or more separate clinic days, or intake of one or more antihypertensive medications. The selected cases had hypertension but without diabetes mellitus or renal failure. The selected controls had the following characteristics: age (within a 5-year range) and gender matched with the cases; SBP < 120 mm Hg and DBP < 80 mm Hg in subjects who were not acutely ill and had no history of elevated BP, diabetes mellitus, kidney disease,
antihypertensive medication use, or family history of hypertension in first-degree relatives.

**Study Protocol**

On the test day, after an overnight fast and withholding of antihypertensive medication for at least 12 hours, the subjects were admitted at 8:00 AM to the laboratory of the Fuyang People’s Hospital. Basic information on the subjects was collected, and anthropometric variables, such as height, weight, and BP were measured. Body mass index, defined as weight (kg) per height squared (m$^2$), was calculated. Following baseline blood sample collection (T0 min), the subjects consumed a standard mixed breakfast of about 50 kJ (18% protein, 20% fat, and 60% carbohydrate) over a 30-minute period. Blood samples were collected, and BPs were measured at 30, 60, and 120 minutes after the meal ingestion.

**Serum Gastrin, Renin, Aldosterone, Angiotensin I, and Angiotensin II Analyses**

The samples were collected into chilled tubes containing 1.2 mg EDTA and aprotinin (500 KIU/mL; Trasylol; Bayer Corporation, Leverkusen, Germany) for hormone analyses. All samples were kept in an ice bath until centrifugation at 2000 rpm for 15 minutes at 4°C. Serum gastrin was measured using an iodine [125I] Gastrin Radioimmunoassay Kit (Beijing North Institute of Biological Technology, Beijing, China). Renin, aldosterone (Ald), angiotensin (Ang) I, and Ang II were measured using an iodine [125I] Angiotensin I Radioimmunoassay Kit, iodine [125I] Aldosterone Radioimmunoassay Kit, and iodine [125I] Angiotensin II Radioimmunoassay Kit (Beijing North Institute of Biological Technology). The total cholesterol (TC), high-density lipoprotein cholesterol, and triglyceride (TG) levels were measured using spectrophotometrical method developed by Fuyang People’s Hospital. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula.

**Statistical Analysis**

Data were analyzed with Sigma Stat 3.0 (Systat Software Inc., Chicago, IL, USA) and expressed as mean ± SEM. Comparison between three or more groups was performed by two-way ANOVA (analysis of variance), followed by post hoc analysis using the Tukey’s multiple comparison test; t test was used to compare between two groups. The correlation between gastrin and other hormones was analyzed with the Pearson correlation test. Differences between means were considered as statistically significant at $P < .05$.

**RESULTS**

**Basic Characteristics**

A total of 177 subjects were investigated, including 95 hypertensives (HT) and 82 normal controls (NT). As shown in Table 1, Ald, Ang II, TC, and TG levels are higher in hypertensives than normal controls ($P < .05$), but renin, LDL-C, and Ang I levels are similar in HT and NT. The total cholesterol, triglycerides, and low-density lipoprotein-cholesterol levels are in normal range in both groups. There is also no difference in basal serum gastrin levels between the two groups.

**BP Response to the Test Meal**

Table 2 shows that fasting BPs are significantly higher in HT than NT ($P < .05$). In the hypertensives group, the BP significantly decreases after the meal and remains decreased, relative to fasting values, 120 minutes after eating. Food intake does not change the BP in NT.

**Gastrin Response to the Test Meal**

As shown in Figure 1, the fasting patterns of the postprandial increase (peak at 30 min) in serum gastrin levels are similar in HT and NT. However, the gastrin levels at 30, 60, and 120 minutes are significantly higher in HT than NT ($P < .05$, t test).

**Correlation Between Basal Serum Levels of Gastrin and Other Hormones**

As shown in Table 3, fasting serum levels of gastrin are significantly correlated with fasting serum levels of Ald and Ang II ($P < .05$, Pearson correlation test) in HT but not NT. There is no correlation between gastrin and renin in either group.

**DISCUSSION**

The results of this study show that postprandial serum gastrin levels increase in both hypertensive and normotensive adults. The fasting serum gastrin levels are similar in the two groups. However, the postprandial gastrin levels are higher in hypertensive adults than normotensive adults. We also find that the postprandial BPs in
levels in normotensive adults is not associated with an increase in BP. The activity of the sympathetic nervous system is increased in hypertensive subjects (13). Gastrin can produce anxiety and increase sympathetic nerve activity (14). Thus, the increase in circulating gastrin levels after a meal cannot explain the acute decrease in BP in hypertensive subjects.

The chronic regulation of BP is related to sodium balance and sodium distribution in extracellular fluid compartments (15,16). Hypertension develops when sodium accumulates with continued sodium intake and can no longer be excreted (15,16), extracellular fluid expands, and/or compensatory neural (17), hormonal, and pressure natriuresis (18,19) mechanisms fail. Epidemiological and intervention studies have demonstrated a clear relationship between salt intake and hypertension (20). Cholecystokinin B receptor, the receptor for gastrin, is expressed in the proximal tubule and the distal collecting duct in human and nonhuman kidneys (21). It has been suggested that after a meal, gastrin is released into the circulation and occupies the CCKBR in the kidney to decrease sodium transport, enabling the excretion of the sodium load (3), a mechanism that is not associated with an increase in BP (15), as is the case in this report. Indeed, in our hypertensive subjects, BPs are decreased after eating. The increase in sodium excretion after a meal could be related to an acute inhibition of sodium transporting mechanisms, including a decrease in activity of the renal Na/K-ATPase (22). Cell signal transducers of many G protein-coupled receptors, including gastrin, may regulate the activity of Na/K-ATPase (22–24). Agonists such as gastrin (22) can increase the expression or activity of cell signal transducers such as protein kinase C (PKC) and protein kinase A (PKA) to directly or indirectly regulate Na/K-ATPase activity. Our preliminary studies have also shown that gastrin acutely decreases renal Na/K-ATPase activity (3). The inhibitory effect of hormones on Na/K-ATPase activity may be direct or indirect via inhibition of NHE3 (Sodium/hydrogen exchanger type 3) activity (25–29). Several enterokines, including cholecystokinin (1,3,4) and gastrin (1–3), have been suggested to be

Table 2. Comparison of pre- and post-prandial BPs between HT and NT

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Postprandial</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>30 min</td>
</tr>
<tr>
<td><strong>NT (n = 82)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>116.3 ± 0.2</td>
<td>113.5 ± 0.1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80.4 ± 0.1</td>
<td>76.6 ± 0.11</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>92.3 ± 0.1</td>
<td>88.9 ± 0.1</td>
</tr>
<tr>
<td><strong>HT (n = 95)</strong></td>
<td>148.1 ± 0.4</td>
<td>141.2 ± 0.4*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>96.2 ± 0.4</td>
<td>90.4 ± 0.3*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>113.5 ± 0.4</td>
<td>107.3 ± 0.3*</td>
</tr>
</tbody>
</table>

Abbreviations: BP – blood pressure; DBP – diastolic blood pressure; HT – hypertensives; MAP – mean arterial pressure; NT – normal controls; SBP – systolic blood pressure.

Fasting and 30, 60, and 120 min postprandial BPs in hypertensive (HT) and normotensive adults (NT). The values are expressed as mean ± SEM.

*P < .05 versus fasting values (one-way ANOVA, Tukey’s test).

In addition, our preliminary studies have also shown that gastrin acutely decreases renal Na/K-ATPase activity (3). The inhibitory effect of hormones on Na/K-ATPase activity may be direct or indirect via inhibition of NHE3 (Sodium/hydrogen exchanger type 3) activity (25–29). Several enterokines, including cholecystokinin (1,3,4) and gastrin (1–3), have been suggested to be

Table 3. Correlation between basal serum concentrations of gastrin and Ang II, Ald, or renin

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ang II</th>
<th>Ald</th>
<th>Renin</th>
</tr>
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<tbody>
<tr>
<td>HT</td>
<td>0.235*</td>
<td>0.239*</td>
<td>0.061</td>
</tr>
<tr>
<td>NT</td>
<td>0.070</td>
<td>0.077</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Abbreviations: Ald – aldosterone; Ang II – angiotensin II; HT – hypertensives; NT – normal controls.

*P < .05 (Pearson correlation test).

hypertensive adults are decreased and are correlated with the higher postprandial gastrin levels. Postprandial hypotension (fall in SBP ≥ 20 mm Hg within 2 hours of eating a meal) occurs in some patients with hypertension but more frequently in certain risk groups (e.g., Parkinson’s disease, autonomic failure) and elderly individuals (10). In healthy adults, postprandial SBP is not regularly affected but DBP may be minimally decreased (11). A role of hormones released with food intake and gastric distention on acute changes in cardiovascular function has not been proven. However, the intravenous injection of pentagastrin does not affect BP in normotensive humans (12). This is consistent with our study; the increase in postprandial gastrin levels in normotensive adults is not associated with an increase in BP. The activity of the sympathetic nervous system is increased in hypertensive subjects (13). Gastrin can produce anxiety and increase sympathetic nerve activity (14). Thus, the increase in circulating gastrin levels after a meal cannot explain the acute decrease in BP in hypertensive subjects.

In the current report, we have also shown that gastrin acutely decreases renal Na/K-ATPase activity (3). The inhibitory effect of hormones on Na/K-ATPase activity may be direct or indirect via inhibition of NHE3 (Sodium/hydrogen exchanger type 3) activity (25–29). Several enterokines, including cholecystokinin (1,3,4) and gastrin (1–3), have been suggested to be
involved in the inhibition of renal sodium transport after a meal. However, circulating levels of gastrin are 10–20-fold higher than cholecystokinin (30) and the renal uptake of gastrin is greater than the other enterokines released after a meal (31). Gastrin could also inhibit epithelial sodium channel (ENaC) activity in the collecting duct where CCKBRs are expressed to regulate pressure natriuresis (6). The dysregulation of the ability of a humoral agent to decrease intestinal and renal and sodium transport, such as gastrin, may be a mechanism in the development of hypertension (28,32,33).

The renin–angiotensin–aldosterone system (RAS) is recognized as the body’s most powerful hormone system for controlling BP (34). In this study, we find that fasting ald and Ang II levels are higher in hypertensive adults than normotensive adults. In addition, the ald and Ang II are positively correlated with fasting serum gastrin levels in hypertensive but not normotensive adults. Angiotensin II may indirectly decrease gastrin function (35). Food intake which distends the stomach releases gastrin (36) and gastric distention activates the RAS (37), suggesting that gastrin may stimulate the RAS with negative feedback inhibition of gastrin release by Ang II. However, gastrin does not stimulate renin secretion in normotensive humans (38). In addition, gastric distention may not be the cause of the increase in gastrin release with food intake (unpublished studies). Moreover, the positive correlation between gastrin and Ang II is found in fasting samples and the relationship between postprandial gastrin and Ang II levels was not examined. Therefore, any interaction between the RAS and the gastrin in the regulation of BP could not be determined in this study.

In summary, we found that the gastrin levels increase to higher levels in hypertensive adults than normotensive adults, in spite of similar fasting gastrin levels. The higher fasting circulating ald and Ang II concentrations in hypertensive than normotensive adults are positively correlated with fasting serum gastrin levels. We suggest that gastrin is involved in the regulation of BP via the regulation of sodium and water metabolism and/or RAS, especially in hypertension. However, the mechanism of this regulation remains to be determined.

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REFERENCES


