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Role of bradykinin in postprandial hypotension in humans

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Abstract

A transient significant decrease in mean arterial blood pressure (MAP) from 107 ± 3 to 98 ± 3 mmHg (P<0.05) was observed in elderly (59-69 years of age), healthy volunteers 25-30 min following ingestion of a test meal. In young volunteers (22-34 years of age), a postprandial decrease of MAP from 88 ± 3 to 83 ± 4 mmHg was also noted but it was not statistically significant. A 40% decrease in bradykinin (BK) content of circulatory high molecular weight kininogen had previously been observed in human subjects given the same test meal. We presently demonstrate by specific ELISA that the stable pentapeptide metabolite (1-5 BK) of BK increases from 2.5 ± 1.0 to 11.0 ± 2.5 pg/ml plasma (P<0.05) in elderly volunteers and from 2.0 ± 1.0 to 10.3 ± 3.2 pg/ml plasma (P<0.05) in young volunteers 3 h following food intake. This result suggests that ingestion of food stimulates BK release from kininogen in normal man. Postprandial splanchnic vasodilatation, demonstrated by a decrease of plasma half-life of intravenously administered indocyanine green (ICG), a marker of mesenteric blood flow to the liver, from 4.4 ± 0.4 to 3.0 ± 0.1 min (P<0.05) in young volunteers and from 5.2 ± 1.0 to 4.0 ± 0.5 min (P<0.05) in elderly volunteers, accompanied BK release. The participation of BK in this response was investigated in subjects given the BK-potentiating drug captopril prior to food intake. Postprandial decreases of ICG half-lives were not changed by this treatment in either young or elderly subjects, a result which may indicate that BK released following food intake plays no role in postprandial splanchnic vasodilatation in normal man.

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Key words
- Bradykinin
- Postprandial hypotension
- Indocyanine green
- Captopril
- 1-5 Bradykinin

Introduction

Bradykinin (BK) modulates vascular tone as a direct effect and as a stimulant of nitric oxide release from the vascular endothelium. The importance of the participation of BK in the control of mesenteric vascular tone has been emphasized (1). BK content of high molecular weight kininogen (HMWK) in plasma is decreased following food intake in healthy volunteers (2,3), suggesting that BK released by alimentary stimulation may contribute to postprandial hypotension by causing vasodilatation at the splanchnic level (3). In the present investigation, postprandial BK release was studied by measuring by

specific ELISA the circulating amounts of the 1-5 BK pentapeptide, a metabolic product considerably more stable than BK (4,5), following ingestion of a test meal by healthy volunteers.

The measurement of changes in the circulatory half-life ($t_{1/2}$) of intravenously administered indocyanine (cardio)-green (ICG), a dye which is fully and rapidly taken up by the liver, offers a simple and reliable means of assessing splanchnic (mostly mesenteric + hepatic) blood flow (6,7). In order to test the hypothesis that BK contributes to postprandial splanchnic vascular changes, ICG was employed to determine whether the BK-potentiating drug captopril potentiates the decrease in splanchnic blood flow evoked by food intake.

Material and Methods

Subjects

Six young males (22-34 years of age) with a body mass index of 24.4 ± 1.7 kg/m^2, and 5 elderly males and 1 elderly female (59-69 years of age) with a body mass index of 26.2 ± 2.6 kg/m^2, presenting values of arterial blood pressure (BP) normal for their age, participated in this study. No subject showed evidence of chronic or intercurrent illness or was taking medication. Subjects agreed to a 15-h overnight fast on the eve of their admission to the hospital of the Medical School of Ribeirão Preto, and gave informed consent to participate in the planned experimental procedures, which were approved by the Review Board for Human Research of the Hospital.

Assays

With the subject at rest in a reclining hospital bed, a catheter was inserted into a forearm vein for blood sampling. Another catheter was inserted into a contralateral cubital vein for infusion of test solutions. After a period of rest of 30 min, systolic and diastolic arterial BP were measured at 5-min intervals using the arm cuff technique. Mean arterial blood pressure (MAP) was calculated as one third of the difference between systolic and diastolic plus diastolic BP.

To study the effects of food intake, a test meal of 250 ml of Sustagen (Mead-Johnson Nutritionals, São Paulo, Brazil), containing 240 cal (45 g carbohydrate, 14 g protein and 13 g fat), was ingested by the subjects over a period of 5 min.

The bradykinin metabolite R'PPGF^5 (1-5 BK) was assayed by enzyme-linked immunosorbent assay (ELISA) using an analytical kit (Markit M 1-5, Dainippon, Osaka, Japan) containing an anti-bradykinin-pentapeptide antibody which does not cross-react with intact BK or its octa- and hepta-peptide metabolites (4,5). Changes in circulatory levels of 1-5 BK were followed by comparing the amounts present in plasma of subjects after a fast and 1, 2, and 3 h following food intake.

Splanchnic blood flow was assayed by determining (7) the plasma $t_{1/2}$ of ICG in subjects prior to and following ingestion of the test meal. Four minutes after intravenous injection of 2.5 ml of a 5 mg/ml solution of ICG (Cardiogreen, Becton-Dickinson, Corkeysville, MD, USA), six 3-ml samples of blood were collected every 2 min from the fasted subjects, and after two periods starting 11 and 26 min following ingestion of the test meal; all three series of blood collections were preceded by administration of the same amounts of ICG. After clotting and centrifugation, the ICG content of serum samples was determined spectrophotometrically at 805 ηm by comparison with a standard solution of the dye in serum. By plotting of plasma ICG concentration against time on a semilogarithmic scale, a straight line was obtained, permitting the calculation of $t_{1/2} = (t_2 - t_1)$ when the corresponding values of circulatory dye concentration were $C_1 = 2C_2$. Postprandial values of $t_{1/2}$ expressed in minutes were averages corresponding to the two periods of measurement.

Captopril (Capoten, Bristol-Myers Squibb, São Paulo, Brazil) was administered *per os* to fasted subjects 1 h prior to experimentation. The 25 mg dose given did not alter basal MAP.

Statistical analysis

Independent groups were compared by the Mann-Whitney test. Paired control and experimental parameters obtained for the same subject were compared by the Wilcoxon signed rank test. $P \leq 0.05$ expressed statistical significance of comparisons.

Results

Figure 1 presents MAP changes following ingestion of a standard test meal by 6 elderly and 6 young volunteers. In the former, alimentation caused MAP to decrease from a fasting value of 107 ± 3 to 98 ± 3 mmHg ($P<0.05$), 25, 30 and 40 min after alimentation; return to control values occurred after 45 min. In young individuals, the decrease in MAP was not statistically significant. A transient increase in MAP was observed 20 min following alimentation of the young group, but not in elderly subjects.

Evidence suggesting that BK may be a factor causing postalimentary hypotension was obtained by demonstrating (Figure 2) that the 1-5 peptide metabolite of BK increased in plasma following food ingestion in both young and elderly individuals; this change, incipient after 1 or 2 h, was statistically significant after 3 h. Control subjects not given the test meal did not present changes in circulatory 1-5 BK after 1, 2 or 3 h.

Figure 3 shows that, following ingestion of food, the plasma half-life of intravenously administered ICG was significantly decreased in both young and elderly volunteers. Table 1 shows that ICG half-lives measured following ingestion of food were unchanged in subjects given captopril prior to alimentation when compared to ICG half-lives of controls given a meal, but not treated with the drug.

Discussion

Twenty-five, 30 and 40 min following ingestion of a test meal, elderly subjects

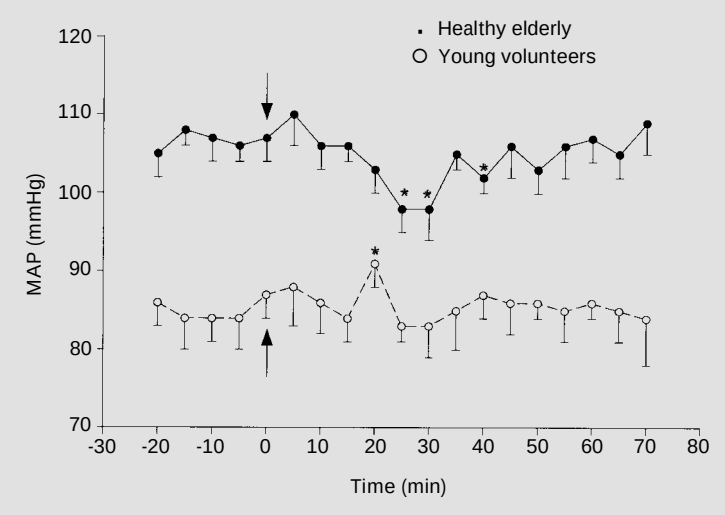

Figure 1 - Mean arterial blood pressure (MAP) of healthy elderly and young volunteers, prior to and following ingestion (arrows) of a test meal. Data are reported as the average ± SEM for 6 subjects. *P≤0.05 for paired comparisons between MAP prior to (0 time), and following food intake (Wilcoxon test).

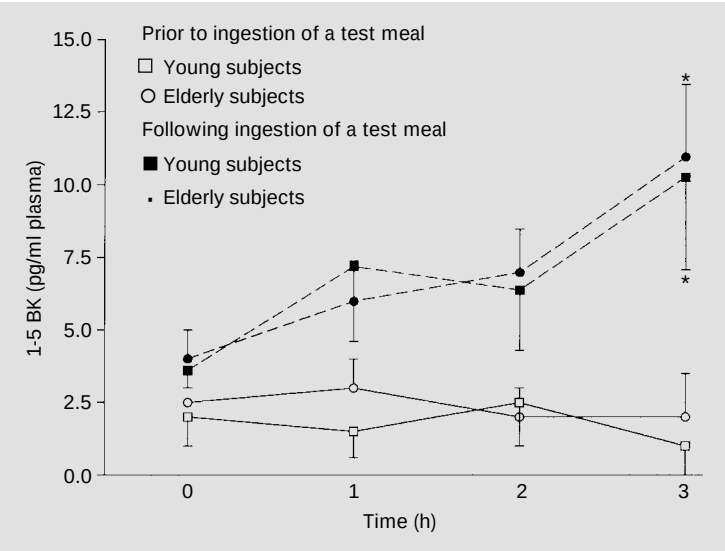

Figure 2 - 1-5 BK peptide metabolite of bradykinin in the circulation of young and elderly subjects prior to or following ingestion of a test meal. Data are reported as the average ± SEM for 6 subjects. *P<0.05 for paired comparisons between plasma 1-5 BK content prior to and following food intake (Wilcoxon test).

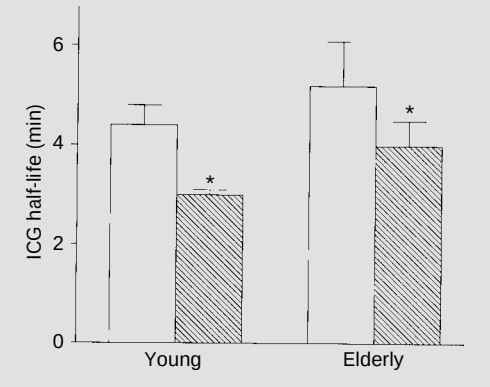

Figure 3 - Indocyanine green (ICG) circulatory half-life in young and elderly volunteers prior to (open columns) or following (hatched columns) administration of a test meal. Data are reported as the average ± SEM for 6 subjects. *P≤0.05 for paired comparisons between half-lives measured prior to and following food intake (Wilcoxon test).

Table 1 - Postprandial indocyanine green half-life ($t_{1/2}$) in young and elderly volunteers prior to and following administration of captopril.

Data are reported as means ± SEM for 6 subjects in each group.

Treatment	$t_{1/2}$ (min)	
	Young subjects (22-34 years)	Elderly subjects (59-69 years)
Test meal	3.0 ± 0.1	4.5 ± 0.5
Captopril (25 mg, *per os*) 60 min prior to test meal	3.4 ± 0.3	4.6 ± 0.3

presented statistically significant decreases in mean arterial blood pressure. Some young subjects also exhibited this response but, as also reported by others (8), systemic postprandial hypotension fails to be statistically significant in this age group. Twenty minutes following alimentation, a transient increase in MAP was observed in young volunteers, most probably reflecting a burst of sympathetic activity evoked by insulin released by the alimentary stimulus (8-10). Elderly individuals did not show this response. It is likely that the delayed or insufficient systemic compensatory baroreflex sympathetic activity known (8-13) to accompany aging is responsible for age-linked differences in postprandial MAP responses.

Increased circulatory levels of the pentapeptide metabolite of BK (1-5 BK) observed following alimentation support the conclusion (2,3,14,15) that a reduced BK content of circulatory HMWK evoked by food indicates BK release.

Circulatory indocyanine green half-life, which reflects splanchnic vascular tone and hepatic blood flow, was significantly decreased following food ingestion. Captopril, a kininase inhibitor of the angiotensin converting-enzyme (ECA) inhibitor group, is capable of potentiating certain responses to BK (16). In the present study, it failed to enhance the effect of alimentation on ICG $t_{1/2}$ in either young or elderly subjects. This finding suggests that BK does not participate in the genesis of postprandial vasodilatation at the mesenteric level. However, this conclusion is open to some objections. The test meal given to our subjects has been shown to cause the release of nearly 0.4 µg of BK from HMWK per ml plasma within 30 min (2,3). It is possible that this rather large amount of BK reaching the mesenteric circulation exerts already maximal vasodilatatory effects which are not increased by captopril, which, in order to avoid systemic hypotensive effects of its own, was administered in the present work in a fairly modest dose. The rapid BK inactivation by the liver even in the presence of captopril (17), may also contribute to preventing the drug from increasing postprandial ICG $t_{1/2}$. Additional experiments using subjects pretreated with specific inhibitors of BK vascular effects to evaluate the participation of BK in postprandial splanchnic and systemic hypotension cannot be carried out because their safety for human subjects has not yet been demonstrated (Colman RW, personal communication).

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