The Second-Meal Phenomenon in Type 2 Diabetes

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OBJECTIVE — In health, the rise in glucose after lunch is less if breakfast is eaten. We evaluated the second-meal effect in type 2 diabetes.

RESEARCH DESIGN AND METHODS — Metabolic changes after lunch in eight obese type 2 diabetic subjects were compared on 3 days: breakfast eaten, no breakfast, and no breakfast but intravenous arginine 1 h before lunch.

RESULTS — Despite comparable insulin levels, the rise in plasma glucose after lunch was considerably less if breakfast had been eaten (0.68 ± 1.49 vs. 12.32 ± 1.73 vs. 7.88 ± 1.03 mmol · h^{-1} · l^{-1}; $P < 0.0001$). Arginine administration almost halved the lunch rise in plasma glucose (12.32 ± 1.73 vs. 7.88 ± 1.03 mmol · h^{-1} · l^{-1}). The plasma free fatty acid concentration at lunchtime directly related to plasma glucose rise after lunch ($r = 0.67$, $P = 0.0005$).

CONCLUSIONS — The second-meal effect is preserved in type 2 diabetes. Premeal administration of a nonglucose insulin secretagogue results in halving the postprandial glucose rise and has therapeutic potential.

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The effect of a prior meal in decreasing the rise in blood glucose after a subsequent meal was first recognized almost a century ago (1). It has repeatedly been confirmed in healthy subjects, but tests with intravenous or oral glucose suggested that the second-meal effect does not occur in type 2 diabetes (2–4). We observed incidentally that a second meal in subjects with type 2 diabetes brought about a 70% lesser rise in blood glucose (5).

This study was designed to determine whether the second-meal phenomenon is present in type 2 diabetes and, if so, whether this can artificially be induced as a possible therapeutic approach.

RESEARCH DESIGN AND METHODS

— Eight subjects with type 2 diabetes were recruited (aged 56.1 ± 2.8 years, BMI 36.0 ± 2.5 kg/m^2, A1C 6.7 ± 0.2%, diabetes duration 8.1 ± 0.5 years, diet and/or metformin treatment). Ethics committee permission was obtained.

Study methods

The metabolic response to a standard lunch was studied on 3 separate days in random order with 2–4 weeks between studies. On day A, the subjects had a standard breakfast followed by the standard lunch. On day B, breakfast was omitted. On day C, breakfast was omitted and arginine was infused 1 h before lunch. The details of metabolic testing, arginine administration, and hormone and metabolites assays were as previously described (5,6).

Meal composition

The standard breakfast consisted of 50 g muesli, 100 g milk, two slices of toast (56 g), 20 g marmalade, 20 g margarine, and 200 ml orange juice (106 g carbohydrate, 18 g fat, 15 g protein, 646 kcal). The standard lunch comprised a cheese sandwich, 200 ml orange juice, 170 g yogurt, and 150 g jelly (103 g carbohydrate, 30 g fat, 44 g protein, 858 kcal).

Statistical analysis

Data are presented as means ± SE. One-way ANOVA and linear correlation were performed using MINITAB (State College, PA).

RESULTS

Glucose

The rise in plasma glucose after lunch was greatest on the day without breakfast and almost 40% lower on the arginine day (0.68 ± 1.49 vs. 12.32 ± 1.73 vs. 7.88 ± 1.03 mmol · h^{-1} · l^{-1}; $P <$ 0.0001) (Fig. 1*A*).

On day A, breakfast increased plasma glucose from 7.6 ± 0.4 to 13.3 ± 1.0 mmol/l at 2 h and 8.4 ± 0.7 mmol/l at 4 h. On day B (no breakfast), plasma glucose fell from 8.0 ± 0.4 to 6.5 ± 0.3 mmol/l by 4 h. Two hours after the test, lunch plasma glucose was 8.6 ± 0.6 mmol/l on day A compared with 10.9 ± 0.8 mmol/l on day B.

On day C, fasting plasma glucose fell from 7.6 ± 0.6 mmol/l to 6.6 ± 0.6 mmol/l at 3 h just before the arginine infusion and was 7.1 ± 0.7 mmol/l at 4 h.

Serum insulin and C-peptide

Fasting serum insulin was similar on each of the days (127 ± 23, 140 ± 48, and 115 ± 27 pmol/l for days A, B, and C, respectively; $P = 0.87$). The post-lunch serum insulin concentrations were comparable on days A, B, and C (1,918 ± 45 vs. 2,040 ± 75 vs. 1,472 ± 40 pmol · h^{-1} · l^{-1}, respectively; $P = 0.76$). On day A, serum insulin peaked at 954 ± 237 pmol/l 2 h after breakfast. On day C, insulin concentrations increased sharply after 30 min of the arginine infusion (418 ± 177 pmol/l) but returned to the baseline (157 ± 37 pmol/l) before lunch.

Insulin–to–C-peptide ratios were similar after the test lunch on all three experimental days (144 ± 23, 185 ± 47, and 168 ± 31 pmol/nmol, respectively; $P = 0.73$ at 2 h after lunch).

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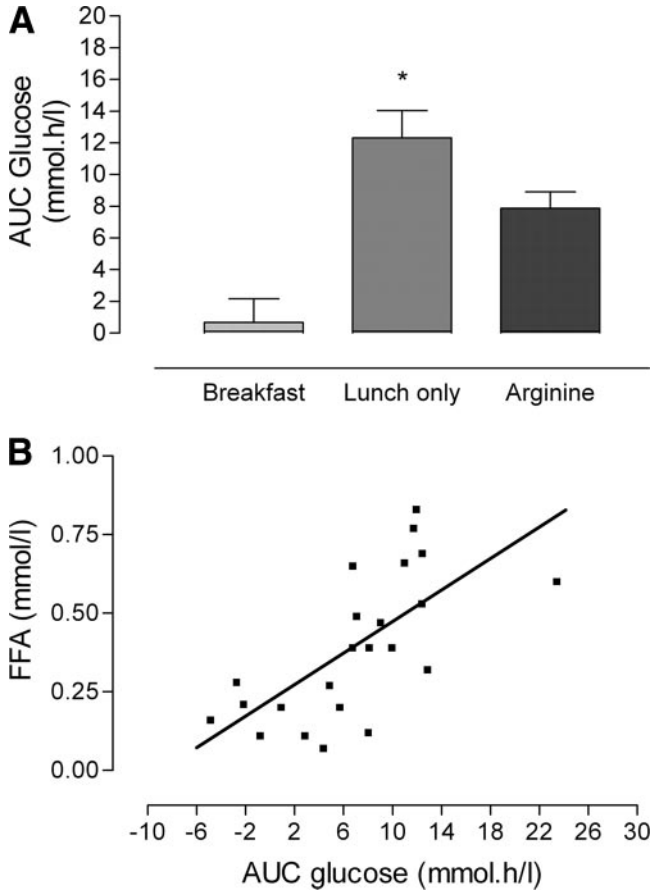

Figure 1—A: *Incremental change in plasma glucose after lunch. *P < 0.0001 area under the curve (AUC; 4-8 h).* B: *Strong positive correlation between lunchtime plasma FFAs and the increase in plasma glucose concentration after lunch (r = 0.67, P = 0.0005) in type 2 diabetes.*

Glucagon and catecholamines

Fasting glucagon levels were similar on each of the three experimental days (87 ± 11, 83 ± 9, and 83 ± 7 pg/ml, respectively). On day C, the arginine infusion induced a threefold increase in glucagon concentrations after 30 min to a short-lived peak of 263 ± 28 pg/ml.

Pre-lunch and 30-min post-lunch adrenaline levels were similar on each day (0.32 ± 0.06, 0.36 ± 0.04, and 0.37 ± 0.04 nmol/l; $P = 0.77$; and 0.34 ± 0.04, 0.41 ± 0.06, and 0.39 ± 0.04 nmol/l, respectively; $P = 0.67$).

Plasma free fatty acids

Fasting plasma free fatty acids (FFAs) were similar on the three study days (0.64 ± 0.07, 0.65 ± 0.9, and 0.67 ± 0.7 mmol/l, respectively; $P = 0.96$). After breakfast on day A, plasma FFA levels were suppressed within 2 h to 0.18 ± 0.04 mmol/l. On day B, plasma FFAs were 0.65 ± 0.4 mmol/l before and 0.27 ± 0.04 mmol/l 2 h after lunch. On day C, plasma FFAs were suppressed by the arginine infusion (0.35 ± 0.04 mmol/l) and the lunch (0.18 ± 0.03 mmol/l 2 h after lunch). The concentration of plasma FFAs was strongly related to the area under the curve of the plasma glucose concentration after lunch ($r = 0.67$, $P = 0.0005$) (Fig. 1*B*).

CONCLUSIONS

— In obese type 2 diabetic subjects, the rise in plasma glucose was 95% less after lunch when the lunch had been preceded by breakfast, confirming the occurrence of the second-meal effect in type 2 diabetes. The effect on plasma glucose was similar or slightly greater than that in healthy subjects (73% decrease in post-lunch hyperglycemia) (7). Substrate oxidation rates were unchanged across experimental days (data not shown). The plasma FFA concentration before lunch correlated positively with the post-lunch rise in plasma glucose after lunch. The post-lunch insulin profiles were similar on all test days.

The concept that the second-meal phenomenon did not occur in type 2 diabetes is derived from study of repeated intravenous glucose (3), although this has a poor effect on insulin secretion (8). In contrast, a mixed meal or injection of amino acids brings about an increase in plasma insulin levels, even in type 2 diabetes (8,9).

The second-meal phenomenon is not mediated by an acute effect on insulin secretion, and FFA suppression must be considered. Increased FFA induces insulin resistance in humans (10,11). Conversely, suppression of plasma FFA by acipimox acutely improves insulin action in type 2 diabetes by increasing glucose storage as muscle glycogen and decreasing hepatic glucose production (9,12,13). An increase in FFAs leads to an inhibition of net hepatic glycogen breakdown and increases gluconeogenesis (14). We recently observed that, in normal subjects, the second-meal phenomenon was associated with increased rates of storage of lunchtime carbohydrate in muscle glycogen (7).

The present data demonstrate that under everyday conditions, postprandial glucose metabolism in type 2 diabetes is facilitated by suppression of plasma FFA concentrations after a previous meal.

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