Circulating Dopamine and C-Peptide Levels in Fasting Nondiabetic Hypertensive Patients

The Graz Endocrine Causes of Hypertension study

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OBJECTIVE—Accumulating evidence supports a potential role for dopamine in the regulation of insulin secretion. We examined the association between circulating dopamine and C-peptide concentrations using data from the Graz Endocrine Causes of Hypertension (GECOH) study.

RESEARCH DESIGN AND METHODS—After 12 h of fasting, we measured plasma dopamine and serum C-peptide levels and established determining factors of insulin secretion in 201 nondiabetic hypertensive patients (mean age 48.1 ± 16.0 years; 61.7% women).

RESULTS—Mean dopamine and C-peptide concentration were 33.4 ± 38.6 pg/mL and 3.1 ± 2.7 ng/mL, respectively. A strong and inverse correlation was observed between dopamine and C-peptide levels ($r = -0.423$, $P < 0.001$). There was no significant relationship between C-peptide, plasma epinephrine, and norepinephrine. C-peptide levels decreased steadily and significantly from tertile 1 of dopamine (3.6 ng/mL [95% CI 2.9–4.1]) to tertile 3 (1.6 ng/mL [1.5–2.7], $P < 0.001$) after multivariate adjustment.

CONCLUSIONS—The inverse association between dopamine and C-peptide highlights the need to evaluate whether dopamine could be effective for modulating endocrine pancreatic function.

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Circulating dopamine is *1*) derived from sympathetic noradrenergic nerves and 2) is synthesized within the adrenal medulla and in amine precursor uptake and decarboxylation cells (i.e., in the kidney and endocrine pancreas) (1).

Accumulating evidence supports a role for catecholamines in the regulation of insulin secretion (2). Lerner and Porte (3) observed the inhibitory effects of epinephrine (and norepinephrine) on the acute pancreatic insulin response to glucose but not during prolonged hyperglycemia. Animal studies documented an inhibition of pancreatic insulin secretion in response to dopamine administration (4). Mice lacking D2 dopamine receptors showed an impaired glucose–related insulin release, which results in glucose intolerance (5).

In view of the evidence for the inhibitory effects of dopamine on insulin secretion, we hypothesize that circulating dopamine is inversely related to C-peptide levels, reflecting prehepatic insulin secretion, in fasting nondiabetic adult hypertensive patients (6).

RESEARCH DESIGN AND METHODS

The Graz Endocrine Causes of Hypertension (GECOH) study population comprises adult diabetic and nondiabetic patients (aged ≥18 years), who have routinely been referred to our outpatient clinic for screening for endocrine hypertension (6). Between February 2009 and November 2011, 224 white study participants were enrolled. Main inclusion criterion was arterial hypertension. The exclusion criteria have been described in the published study protocol (6). Patients taking antipsychotic drugs and/or with diagnosed pheochromocytoma or Cushing's disease, which are both known to have impact on dopamine and insulin secretion, were excluded from the analysis. Finally, after exclusion of 23 patients with diabetes (0.9% with type 1 diabetes and 9.4% with type 2 diabetes classified according to American Diabetes Association criteria), 201 participants remained eligible for the analysis (7). Blood samplings were performed in the morning (8:00–11:00 A.M.) after the patients had been seated for 10 min.

Extensive laboratory and clinical assessments were performed after at least 12 h of fasting. Written informed consent was obtained from all study participants. The GECOH study complies with the Declaration of Helsinki.

Laboratory methods

The laboratory methods have been described in detail in a previous report (6). Measurement of plasma dopamine concentrations was performed using a radioimmunoassay

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(reference value <100 pg/mL, TriCat RIA; DRG International, Marburg, Germany). Epinephrine and norepinephrine were determined by the TriCat-RIA (reference limit <100 and <600 pg/mL, respectively). Serum C-peptide concentrations were determined by a chemoluminescence sandwich immunoassay (ADVIA Centaur; Siemens Healthcare Diagnostics, Tarrytown, NY).

Statistical analysis

Pearson correlation analyses were performed to analyze the associations between circulating C-peptide, dopamine, epinephrine, and norepinephrine levels. One-way ANCOVA followed by Bonferroni post hoc tests was used to compare mean C-peptide values across sex-specific tertiles of the dopamine concentration after consideration of age, BMI, HbA_{1c}, fasting glucose, triglycerides, LDL cholesterol, HDL cholesterol, serum albumin, C-reactive protein, systolic blood pressure, glomerular filtration rate, epinephrine, norepinephrine, serum cortisol, active smoking, regular alcohol consumption, and detailed antihypertensive medication and statin use as potential confounders. All data were analyzed using the SPSS software package (version 17.0; SPSS, Chicago, IL). $P < 0.05$ was considered statistically significant.

RESULTS—The mean age of the 201 nondiabetic hypertensive white study participants (61.7% women) was 48.1 ± 16.0 years. Plasma dopamine concentration was 33.4 ± 38.6 pg/mL, and serum C-peptide concentration was 3.1 ± 2.7 ng/mL.

Pearson correlation analysis revealed a strong and inverse association between C-peptide and dopamine concentrations ($r = -0.42$, $P < 0.001$). Sex-stratified subgroup analysis revealed a strong correlation between C-peptide and dopamine in either sex (Fig. 1*A* and *B*). No significant correlation was seen between C-peptide and norepinephrine ($r = 0.06$, $P = 0.198$) and epinephrine ($r = -0.05$, $P = 0.196$) levels. Circulating dopamine correlated positively with norepinephrine levels ($r = 0.19$, $P = 0.022$). A strong positive correlation was seen between the insulin–to–C-peptide molar ratio (mean 0.07 ± 0.04 pmol/L:pmol/L) and plasma dopamine ($r = 0.30$, $P < 0.001$), although this association might be mainly attributed to the strong correlation between C-peptide and dopamine. Only borderline significance was found between serum insulin and dopamine ($r = -0.16$, $P = 0.057$).

In fully adjusted ANCOVA, we noted a significant decrease in C-peptide values ($P < 0.001$) across increasing values of dopamine concentration (in sex-specific tertiles) in the entire cohort. The absolute mean difference in C-peptide levels between dopamine concentration tertile 1 (3.6 ng/mL) and tertile 3 (1.6 ng/mL) was 2.0 ng/mL.

CONCLUSIONS—We demonstrate that higher dopamine levels are strongly related to lower serum C-peptide values in plasma of 12-h postabsorptive nondiabetic hypertensive patients. The inverse association between C-peptide and dopamine persisted after consideration of multiple confounders. The present observation implicates a potential role for peripheral dopamine in modulating insulin secretion and β-cell function in fasting conditions.

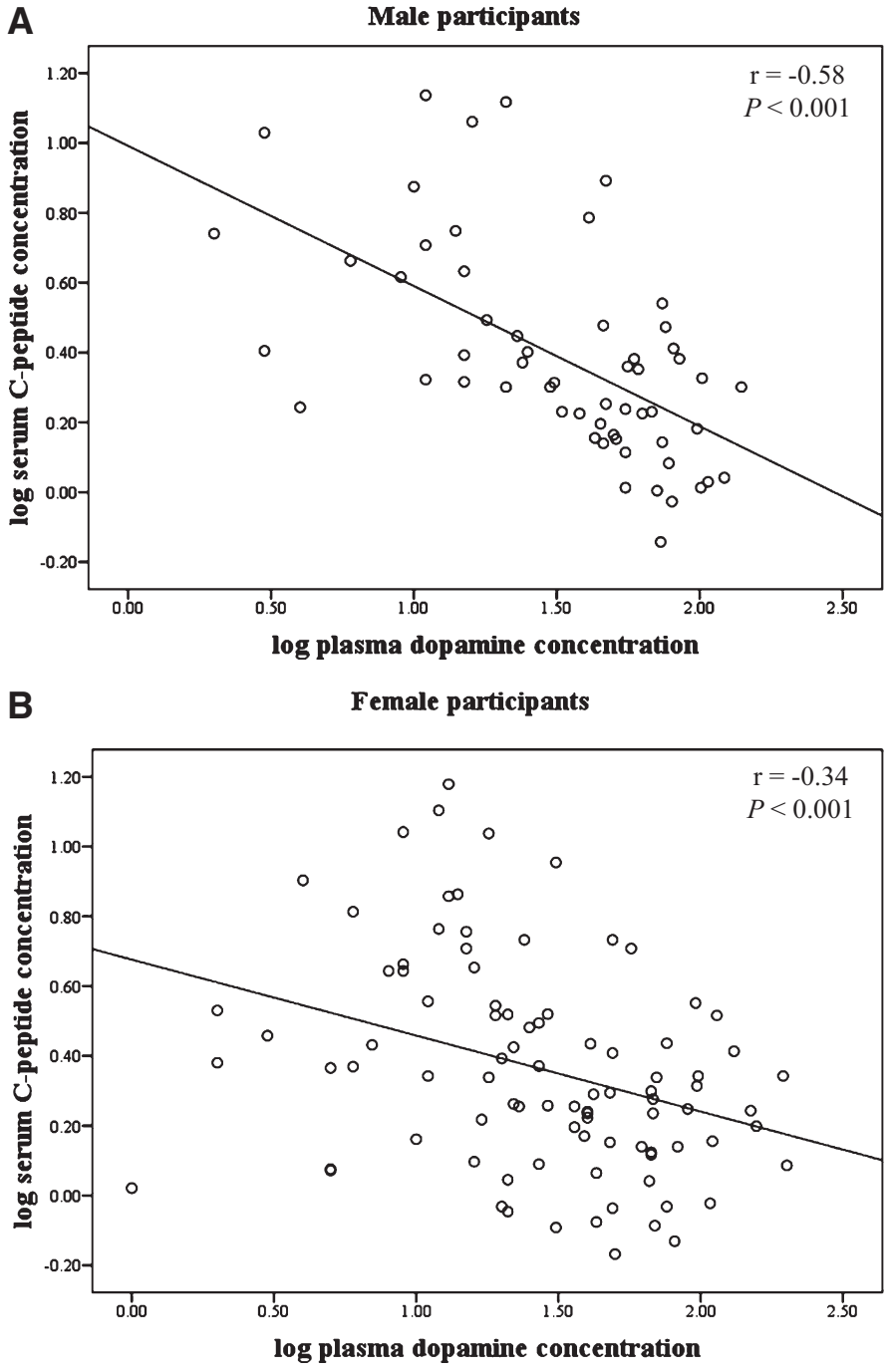

Figure 1—*Scatter plots showing the bivariate Pearson correlation between plasma dopamine and serum C-peptide concentration levels in male* (A) *and female* (B) *participants, respectively.*

There has been growing interest in the impact of dopamine on insulin secretion. Studies in healthy volunteers revealed increased insulin levels after dopamine administration, but these studies were limited by small sample size (8,9). Rubí et al. (4) identified D2 dopamine receptors, which are activated by extracellular (circulating) dopamine, in insulin granules of human β-cells. Activation of these receptors results in an inhibition of glucose-related cell membrane depolarization and insulin exocytosis (4,5,10). Shankar et al. (10) demonstrated that insulin secretion is stimulated at low and inhibited at high dopamine concentrations. These studies therefore, by the majority, support our findings. However, in contrast to previous studies, we neither observed lower dopamine levels nor a weaker association between dopamine and C-peptide levels in diabetic compared with nondiabetic participants (data not shown) (11).

In line with our findings, several human studies documented metabolic alterations by neuroleptic drugs as a result of interference with dopaminergic pathways (12). Several but not all studies documented that the use of the dopamine agonist, bromocriptine, is paralleled by decreased insulinemia (13–15).

We found no association between plasma norepinephrine and serum C-peptide levels. This finding points to dopamine but not to norepinephrine as a major mediator of insulin secretion. Because dopamine, serum cortisol, epinephrine, and norepinephrine clearly were below the upper reference limit, we suggest that our findings are not primarily triggered by an increased stress response.

Although blood was drawn after a 10-min period in the sitting position, we cannot conclude that this resting period was adequate to reliably interpret circulating dopamine levels. In addition, we analyzed nondiabetic hypertensive white subjects; therefore, generalizations to other populations cannot be made. The observational study design precludes conclusions with regard to causal relationships.

In summary, higher circulating dopamine is independently related to lower serum C-peptide. Additional studies are warranted to delineate the effects of dopamine on insulin secretion.

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