Effect of Exogenous Intravenous Administrations of GLP-1 and/or GIP on Circulating Pro-Atrial Natriuretic Peptide in Subjects With Different Stages of Glucose Tolerance

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GLP-1 receptor agonists have antihypertensive properties, explained via release of atrial natriuretic peptide (ANP) as shown in mice (1). Whether GLP-1 directly interacts with the natriuretic peptide system in humans was studied in a single report (2).

Here, we studied interaction of two major incretins, glucose-dependent insulinotropic peptide (GIP) and GLP-1, both administered exogenously, with ANP in patients with type 2 diabetes (nine men and three women, 61 ± 10 years, BMI 30.0 ± 3.7 kg/m^2, HbA_{1c} 7.3 ± 1.5%). Placebo (vehicle: 0.9% NaCl with 1% human serum albumin), GIP (4 pmol · kg^{-1} · min^{-1}), GLP-1(7–36)-amide (1.2 pmol · kg^{-1} · min^{-1}), or a combination of both hormones were infused over 360 min on different days in randomized order (3). Additionally, eight male overweight subjects with normal glucose tolerance (49.9 ± 3.2 years, BMI 32.9 ± 0.7 kg/m^2) were given GIP infusion (2 pmol · kg^{-1} · min^{-1}) and placebo (isotonic saline) infusion for 240 min (4).

In cohort I, intact, biologically active GIP and GLP-1 were measured as described previously (3). In cohort II, total GIP was determined by commercial ELISA kit (Linco Research, St. Charles, MO). Midregional pro-ANP (MR-proANP) was measured with an immunoassay (MR-proANP LIA; B.R.A.H.M.S GmbH, Hennigsdorf, Germany).

In subjects with type 2 diabetes, exogenous GIP elevated the total concentrations of GIP to steady-state levels of ~530 pmol/L and concentrations of intact, biologically active GIP to 225 pmol/L (3). In the experiments with GLP-1 infusion, plasma concentrations of total GLP-1 increased to steady-state levels of ~145 pmol/L and concentrations of intact, biologically active GLP-1 to 20 pmol/L (3). Plasma MR-proANP concentrations decreased with placebo and exogenous GLP-1 administration over the duration of the experiments (Fig. 1*A*). With exogenous GIP, a slight reduction in MR-proANP concentrations was observed in the last hour of the infusion. Coinfusion of GLP-1 and GIP did not further lower MR-proANP concentrations. No difference in MR-proANP concentrations was observed between the experiments.

In healthy overweight subjects, total GIP plasma concentrations during infusion were ~120 pmol/L compared with ~5 pmol/L during saline infusion. MR-proANP concentrations decreased with placebo and exogenous GIP infusion over the duration of the experiments (Fig. 1*B*). No difference in circulating MR-proANP levels between GIP and placebo infusion was observed.

We show that pharmacological doses of GIP and GLP-1, alone or in combination, are unable to stimulate ANP secretion, measured as circulating MR-proANP in subjects with type 2 diabetes. In healthy overweight volunteers, a time course of MR-proANP changes toward lower concentrations during the tests. Our results confirm in part a recently published report on the exogenous application of GLP-1 in healthy men (2). Thus, the GLP-1–ANP axis seems to be species-specific (observed solely in mice) (2). Moreover, decreases in MR-proANP levels were observed during a meal test (5), which may reflect the regulation of MR-proANP by other meal-related factors different from known incretin hormones or diurnal changes of natriuretic peptide levels throughout the day. Limitations of our study are the rather small number of patients studied and the short duration of exposure to incretins.

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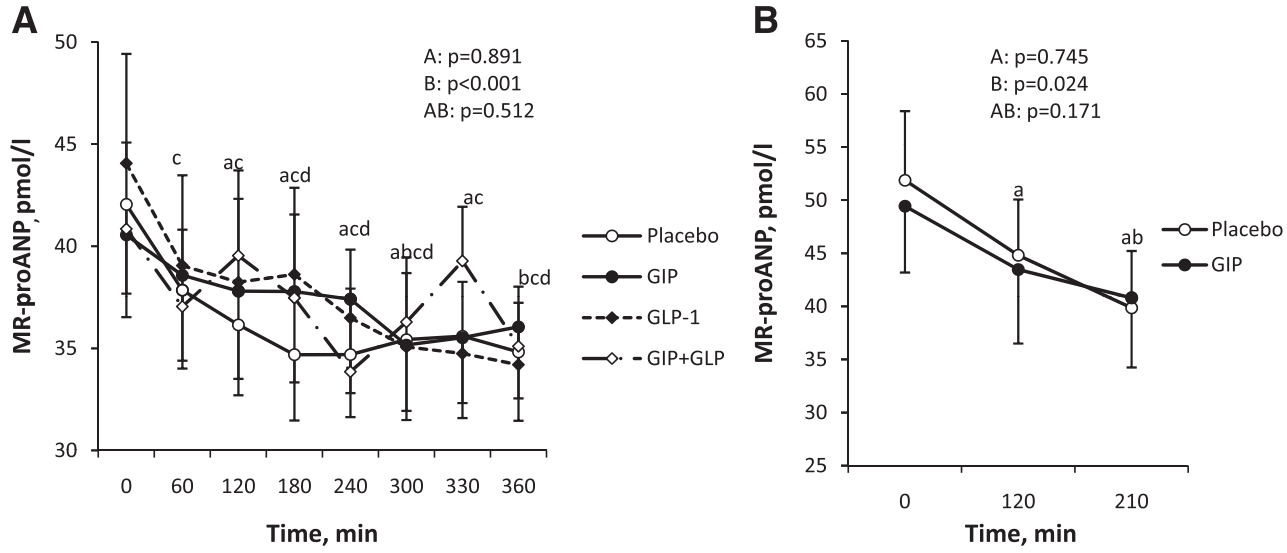

Figure 1—Effects of GIP and GLP-1 infusion on MR-proANP levels. A: Infusion of placebo, GIP, GLP-1, or a combination of both incretin hormones in the cohort I ($n = 12$). B: Infusion of placebo or GIP in the cohort II ($n = 8$). Data are shown as mean ± SE. Statistical analysis was done by two-way repeated-measures ANOVA (A, by treatment; B, by time; AB, interaction of treatment and time). MR-proANP levels at different time points within single treatments were compared by one-way repeated-measures ANOVA. [a]$P < 0.05$ for placebo, [b]$P < 0.05$ for GIP infusion, [c]$P < 0.05$ for GLP-1 infusion, and [d]$P < 0.05$ for GIP + GLP-1 infusion vs. basal MR-proANP level.

In conclusion, our data cannot confirm the existence of an incretin–ANP axis in humans.

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Author Contributions. N.R., M.A.N., and A.F.H.P. were responsible for the conception and design of the study. N.R., O.P., Ö.G., A.S., and M.A.N. conducted the study. N.R., O.P., Ö.G., A.S., W.D., S.D.A., A.M.A., A.B., M.A.N., and A.F.H.P. contributed to acquisition of data, review of data, analysis of data, and discussion of data. N.R. and O.P. were responsible for drafting of the manuscript. O.P., A.S., W.D., S.D.A., A.M.A., A.B., M.A.N., and A.F.H.P. contributed to the critical revision of the manuscript for important intellectual content. N.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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