Acarbose treatment enhances mid-regional pro-atrial natriuretic peptide concentrations in non-diabetic individuals: further evidence for a common cardiometabolic pathway?

N. Rudovich · O. Pivovarova · A. Traberth · A. Sparwasser ·
M. O. Weickert · W. Bernigau · A. L. Birkenfeld ·
A. M. Arafat · A. Bergmann · A. F. H. Pfeiffer

Received: 22 June 2012 / Accepted: 10 August 2012 / Published online: 20 September 2012
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Keywords Acarbose · Mid-regional pro-atrial natriuretic peptide · Type 2 diabetes

Abbreviations

CVD	Cardiovascular disease
MR-proANP	Mid-regional pro-atrial NP
NP	Natriuretic peptide
proANP	Pro-atrial natriuretic peptide
STOP-NIDDM	Study to Prevent NIDDM

To the Editor: Heinisch et al reported that acute infusion of B-type natriuretic peptide (NP) enhances the initial glucose distribution, resulting in a decrease of postload glucose

concentrations by beta cell-independent mechanisms in healthy individuals [1]. This study added to growing evidence regarding a close pathophysiological link between NPs and metabolic traits in obesity, type 2 diabetes and associated diseases [2]. The mechanisms by which NP regulates glucose metabolism are not fully understood, but a reciprocal relationship between glucose regulation and NP has been suggested in type 2 diabetes and cardiovascular diseases (CVDs) [1, 2]. In addition, we and others observed the same type of relations between insulin and NP in obesity [3, 4]. Previous large-cohort observations such as the Study to Prevent NIDDM (STOP-NIDDM) [5, 6] indicate that reduction of postprandial glucose load may be involved in the prevention of both type 2 diabetes and incident hypertension, pointing to a potential ‘bi-directional relationship’

N. Rudovich (✉) · O. Pivovarova · A. Traberth ·
M. O. Weickert · A. F. H. Pfeiffer
Department of Clinical Nutrition,
German Institute of Human Nutrition Potsdam,
Arthur-Scheunert-Allee 114–116,
14558 Nuthetal, Germany
e-mail: rudovich@dife.de

N. Rudovich · O. Pivovarova · A. Traberth · M. O. Weickert ·
A. L. Birkenfeld · A. M. Arafat · A. F. H. Pfeiffer
Department of Endocrinology, Diabetes and Nutrition,
Charité Universitätsmedizin Berlin,
Campus Benjamin Franklin,
Berlin, Germany

A. Sparwasser · A. Bergmann
Thermo Fisher Scientific,
BRAHMS (part of Thermo Fisher Scientific),
Biotechnology Centre Hennigsdorf,
Berlin, Germany

M. O. Weickert
Warwickshire Institute for the Study of Diabetes,
Endocrinology and Metabolism,
University Hospitals Coventry and Warwickshire,
Coventry, UK

M. O. Weickert
Division of Metabolic & Vascular Health,
Warwick Medical School, University of Warwick,
Coventry, UK

W. Bernigau
Department of Epidemiology,
German Institute of Human Nutrition Potsdam,
Nuthetal, Germany

between metabolic and cardiovascular pathways. Unfortunately, STOP-NIDDM was not designed to characterise the mechanisms of acarbose action.

We here investigated whether acarbose-induced modulation of postprandial glucose levels affects mid-regional pro-atrial NP (MR-proANP), which is a stable fragment of N-terminal pro-atrial NP (proANP). This was a single-centre double-blind randomised placebo-controlled crossover study in individuals with different stages of glucose tolerance (Fig. 1; registered trial number ISRCTN40281673; the complete information regarding participants' allocation, primary outcome and side effects has previously been published in Rudovich et al [7]). Following a wash-out period of glucose-lowering medication for at least 3 weeks, the participants were randomised to one of two interventions: placebo–acarbose ($n=32$) and acarbose–placebo ($n=31$). Four individuals discontinued the study because of dissatisfaction with the allocated intervention or lack of time to participate. Three individuals were excluded because of adverse events (gastro-intestinal discomfort, all receiving acarbose treatment), and one was excluded because of a drug-unrelated serious adverse event (ischaemic insult). Thus, 55 participants ($n=20$ individuals with type 2 diabetes; $n=35$ individuals without diabetes) were eligible for the final analyses.

Fig. 1 Study design and participants' disposition. This was a single-centre double-blind randomised placebo-controlled crossover study in individuals with different stages of glucose tolerance. Placebo and acarbose were administered in the same manner. (S)AE, (serious) adverse effect; TID, three times daily

The study protocol was approved by the ethical committees of Potsdam University and Brandenburg, Germany. All study participants gave informed consent. Details of recruitment and phenotyping (individuals with type 2 diabetes/individuals without diabetes: age $60.7 \pm 9.4/57.0 \pm 5.4$ years, $47.4/44.4\%$ female and $52.6/55.6\%$ male, BMI $31.9 \pm 5.5/31.4 \pm 3.1$ kg/m², waist circumference $105.1 \pm 13.7/102.4 \pm 7.8$ cm and HbA_{1c} $6.2 \pm 0.8/5.7 \pm 0.5\%$) of study participants were published recently [7]. Eligible patients were randomised to receive either acarbose (300 mg/day in three divided doses; Glucobay, BayerVital, Leverkusen, Germany) followed by placebo or vice versa, with each administered for 12 weeks, with a 12 week wash-out between interventions. Liquid-meal challenge tests were performed for 240 min using a commercial preparation (Biosorb Energie; Pfrimmer Nutricia, Erlangen, Germany; 77.6 g carbohydrate, 22.3 g fat, 24 g protein, 2,510 kJ per 400 ml) after a 12 h overnight fast. In accordance with the treatment period, either 100 mg acarbose or placebo was given immediately at the start of the meal challenges. Pre-treatment experiments were conducted without drug exposition. Further venous blood samples for the analysis of hormones and blood glucose were taken at -20, -10, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min, timed from ingestion of the meal. Changes in fasting MR-proANP were measured using an immunoassay (MR-proANP immunoluminometric assay (LIA); BRAHMS, Hennigsdorf, Germany).

Individuals with type 2 diabetes had higher HbA_{1c} levels and postprandial glycaemic responses, but the anthropometric data and lipid profiles were not different between the groups (data not shown). During the 12 weeks of treatment, no significant changes in body weight were observed with exposure to placebo or acarbose (Table 1). Nevertheless, all analyses of acarbose effects were adjusted for changes in body weight. Fasting blood glucose and insulin levels remained unchanged during acarbose treatment in both groups (data not shown). As expected, a moderate but significant reduction of postprandial glycaemia by acarbose was observed during the liquid-meal tests (Table 1). The effect on postprandial blood glucose levels was accompanied by a decrease in postprandial insulin concentrations during acarbose treatment (Table 1). In individuals without diabetes, fasting levels of MR-proANP increased after 12 weeks of acarbose treatment (median [range] 23.6% of baseline [from +37.1 to +12.7%], $p=0.001$; Table 1). Moreover, changes in fasting MR-proANP levels (week 0–week 12) correlated negatively with changes in the incremental AUC $\Delta\text{AUC}_{\text{insulin}}(\text{week 0--week 12})$ ($r=-0.53$, $p<0.0001$) and with changes in $\Delta\text{AUC}_{\text{glucose}}(\text{week 0--week 12})$ was observed ($r=-0.32$, $p=0.02$). In individuals with type 2 diabetes, changes in fasting MR-proANP levels failed to reach significance. This was probably related to reduced power in

Table 1 Effects of acarbose treatment on body weight, postprandial glycaemic and insulinogenic response and fasting MR-proANP levels in non-diabetic participants ($n=35$) and participants with type 2 diabetes ($n=20$)

Variable/marker	Placebo		Acarbose		<i>p</i> value ^a
	Baseline (week0)	End of treatment (week 12)	Baseline (week0)	End of treatment (week 12)	
Non-diabetic participants (<i>n</i> =35)					
Body weight (kg) ^b	88.5±14.3	88.6±14.5	90.0±13.3	88.4±14.3	0.054
AUC _{glucose} (0–240 min) (mmol/l×min)	230.3±168.1	197.4±133.3	208.4±187.2	124.6±152.8	0.014
AUC _{insulin} (0–240 min) (pmol/l×min [×10 ³])	63.5±43.1	65.8±37.2	68.0±37.3	41.6±25.2	<0.001
Fasting MR-proANP (pmol/l)	60.8±30.1	53.8±29.0	54.9±28.8	63.9±29.3	0.001
Participants with type 2 diabetes (<i>n</i> =20)					
Body weight (kg) ^b	91.6±16.5	91.3±15.7	92.4±15.8	91.5±15.9	0.421
AUC _{glucose} (0–240 min) (mmol/l×min)	372.3±213.8	363.9±273.6	409.6±227.9	251.4±211.3	0.034
AUC _{insulin} (0–240 min) (pmol/l×min [×10 ³])	80.0±55.5	90.0±120.4	76.8±52.1	61.8±40.5	0.307
Fasting MR-proANP (pmol/l)	75.7±30.5	70.2±23.4	67.0±24.4	73.9±29.2	0.095

Values are mean±SD

Mixed linear models include participant as random factor, treatment type (acarbose or placebo), treatment sequence (acarbose followed by placebo or vice versa), the period effect, the baseline levels of each treatment period and changes in the body weight ($t_{12}-t_0$) as covariates

^a Level of significance based on differences in treatment effects between interventions, evaluated by comparisons of end-of-treatment levels from both treatment periods with that of the first-period baseline

^b Mixed linear models include participant as random factor, treatment as fixed factor and values at week 0 as covariates

this smaller subgroup, though a potential influence of treatment e.g. with metformin on MR-proANP levels cannot be finally excluded (Table 1).

Treatment with acarbose led to an increase in MR-proANP levels in individuals without diabetes that was strongly correlated with a reduction of postprandial insulin and glucose levels. Thus, although the observed acarbose-induced increase in circulating MR-proANP levels was relatively small, it still may contribute to assumed cardioprotective and antihypertensive effects of this drug, as indicated by results from the STOP-NIDDM study, and may provide further evidence for the existence of a ‘common cardiometabolic pathway’ [1, 2].

We observed no significant changes in body weight, insulin sensitivity or markers of systemic inflammation in the present study during the 3 month acarbose treatment [7], supporting that treatment with acarbose might have influenced the observed upregulation of MR-proANP via changes in postprandial insulin responses, and further indicating a potential direct role of insulin in the regulation of ANP-secretion and/or clearance [3].

Given the careful selection of our study participants, all participants had comparable insulin sensitivity and seemed to be in good glycaemic control [7]; we were, however, unable to demonstrate a significant increase in MR-proANP in the individuals with type 2 diabetes, possibly because of the short treatment time, issues related to reduced power in this subgroup, and potential effects of pre-treatment with other drugs

such as metformin. Another explanation may be loss of insulin-dependent regulation of ANP in individuals with diabetes. Further studies are needed to investigate the potential relation between glucose and insulin-modulating effects of glucose-lowering drugs and their consequences regarding the NP system and potential prevention of CVD.

Trial registration International Standard Randomised Controlled Trial Number Register ISRCTN40281673

Acknowledgements We thank all study participants for their cooperation. We gratefully acknowledge the technical assistance of A. Wagner, M. Hannemann, K. Sprengel, S. Baeker, J. Bogusch, A. Herzberg, U. Zingler and J. Inderthal.

Funding The study was supported in part by grants from the Bundesministerium für Bildung und Forschung (MGP 0313042C/NR, MOW, AFHP), from Bayer Vital, Leverkusen, Germany and from BRAHMS, Berlin-Hennigsdorf, Germany.

Duality of interest A. Sparwasser and A. Bergmann are employees of BRAHMS (part of Thermo Fisher Scientific), Biotechnology Centre, Hennigsdorf, Berlin, Germany, a company that manufactures and holds patent rights on the MR-proANP assay.

Contribution statement NR and AFHP were responsible for the conception and design of study. NR, OP and AT conducted the study. NR, OP, AT, AS, AB, WB, MOW, ALB, AMA and AFHP contributed to the acquisition, review, analysis and discussion of data. NR was responsible for drafting the manuscript. OP, AT, AS, WB, MOW, AB, ALB, AMA and AFHP contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final version.

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