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Acute hyperlipidemia but not hyperhomocysteinemia impairs reflex regulation of the cardiovascular system

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Abstract

Background: Elevated circulating lipids and homocysteine may affect autonomic cardiovascular function by decreasing baroreflex sensitivity (BRS) and cardiovagal outflow and by increasing sympathetic drive.
Methods: To test this hypothesis 25 clinically healthy men (mean age 24 ± 2 years) received 500 ml whipping cream (30% fat) and 0.1 g/kg L-methionine, respectively, at intervals of one week apart to induce hyperlipidemia and hyperhomocysteinemia, respectively. Cardiovascular parameters and endothelial function were assessed before and 2 h after the fat load and before and 4 h after the methionine load, respectively. Cardiovascular responses to sublingual application of a nitrovasodilator and a beta-agonist were also determined.
Results: Hyperlipidemia elicited a significant decline in BRS and an increase in heart rate and sympathetic drive. Reductions in BRS were associated with changes in total cholesterol but not with triglycerides or endothelial function. Autonomic and hemodynamic variables remained unaltered during transient hyperhomocysteinemia although there was a trend to lower BRS. Autonomic and hemodynamic responses to pharmacological vasodilation and beta-adrenoceptor stimulation were preserved under both conditions.
Conclusions: These data provide experimental support for the concept that acute hyperlipidemia but not hyperhomocysteinemia impairs reflex regulation of the circulatory system.

Keywords: Baroreflex sensitivity; Hyperlipidemia; Hyperhomocysteinemia; Sympathetic nervous system

1. Introduction

Baroreflex sensitivity (BRS) is a key index for autonomic regulatory processes of the circulatory system and is a significant prognostic marker for total cardiac mortality in patients with previous myocardial infarction and chronic heart failure [1]. Elevated serum lipid and homocysteine levels are widely known to significantly increase the cardiovascular risk and morbidity [2,3]. There is some indication that hyperlipidemia and hyperhomocysteinemia may confer part of their cardiovascular risk by modulation of the baroreceptor reflex circuit involving sympathetic and parasympathetic fibres to the heart and vasculature [4,5]. We previously showed that the BRS and autonomic cardiovascular control was impaired in patients with severe hypercholesterolemia and this could be partially restored by lipoprotein apheresis [5]. Pharmacological lipid lowering regimens have consistently demonstrated to improve in

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autonomic cardiovascular regulation in patients with hyperlipidemia [6–9]. Inconsistent results, however, come from studies applying intralipid-heparin infusion protocols for acute induction of hypertriglyceridemia showing either no changes or decreased BRS [10,11]. Similar studies on possible neural effects of hyperhomocysteinemia do not exist in humans, although moderately elevated homocysteine levels are prevalent in the general population and its association with cardiovascular disease is generally strong [12]. Very recently it was demonstrated that hyperhomocysteinemia induced dysfunction of cardiovascular autonomic systems in rats, which was associated with increased hepatic oxidative stress [4]. These observations, however, need verification in human subjects since the population-based Hoorn study did not find any association of homocysteine levels with cardiovascular autonomic function [13].

The current study addressed the effects of acute hyperlipidemia and hyperhomocysteinemia on cardiovascular autonomic function. We hypothesised that elevated lipids and homocysteine impair BRS, increase vascular and cardiac sympathetic drive and blunt autonomic responses to pharmacological perturbation of the cardiovascular system.

2. Subjects and methods

2.1. Study population

In twenty-five young lean men (24 ± 2 years) autonomic responses to experimental hypertriglyceridemia and hyperhomocysteinemia were studied. All participants were healthy and free of cardiovascular risk factors. Exclusion criteria were chronic and acute diseases, obesity, intolerance against nitrovasodilators or salbutamol, significant hypotension, migraine, increased ocular pressure (>21 mmHg), current smoking, postoperative conditions, and regular intake of medications and vitamin supplements. All participants received detailed verbal and written information about the study objectives and procedures, and gave written informed consent. The study was approved by the Ethics Committee of the Faculty of Medicine at the Technische Universität Dresden and the study protocol performed with the Declaration of Helsinki.

2.2. Experimental protocol

Each individual was studied four times in a randomized order, with intervals of at least one week between the two interventions always preceded by a day for baseline assessment. The liquid fatty meal consisted of 500 ml whipping cream diluted in 200 ml pineapple juice (100 kcal/200 ml). One hundred milliliters of the cream contained 30 g fat thereof 19.5 g saturated fatty acids. The liquid methionine load consisted of 0.1 g/kg body weight L-methionine powder dissolved in 500 ml apple juice (43 kcal/100 ml). The meals were drunk within 15 min between 6:30 and 7:00 a.m.

Hemodynamic and vascular assessments were performed at the days of baseline assessment after a fasting period of 12 h, and at the days of intervention either 2 h after the fat or 4 h after the methionine load, respectively. No other source of energy was provided during the measurements, but water was allowed ad libitum. The participants did not engage in any physical activity during the test, and exercise had been avoided during 24 h preceding the examination.

2.3. Determination of autonomic function

At each occasion, beat-to-beat blood pressure, respiratory rate and heart rate were simultaneously recorded using a Finometer Pro (Finapres Medical, Amsterdam, NL), a piezo-resistive belt and a 3-channel ECG (sampling frequency 512 Hz, digitalized 12 bit). When a stable baseline was reached, 400 μg of the vasodilator substance glyceryl trinitrate (GTN) and 400 μg of the beta-adrenoceptor agonist salbutamol, respectively, were orally administered in consecutive order at 30 min intervals. Biosignals were continuously recorded over approximately 1 h 30 (30 min Baseline − 30 min GTN − 30 min Salbutamol).

Autonomic parameters and BRS were evaluated before and 5 min after nitroglycerin and 10 min after salbutamol by quantification of spontaneous oscillations in systemic arterial pressure and heart rate using multiple trigonometric regressive spectral (MTRS) analysis (ANS Consult, Freital, Germany; www.ans-consult.de) [14–16]. High frequency (HF) oscillations (0.15–0.4 Hz) of heart rate relate to respiratory sinus arrhythmia and thus to cardiovagal tone. HF oscillations of systolic blood pressure are independent of autonomic activity and therefore not reported. Low frequency (LF) oscillations (0.04–0.15 Hz) of heart rate reflect baroreflex-mediated adjustments to the sinus node encompassing sympathetic and parasympathetic fibres. LF oscillations of systolic blood pressure are primarily related to sympathetically mediated fluctuations in peripheral vasomotor tone. The ratio of LF/HF oscillations of heart rate allows for quantification of the relation between the sympathetic and parasympathetic nervous system. The BRS was calculated as the slope of the linear regression line of coherent pairs of the detected oscillations of R–R interval and systolic blood pressure (cross correlation coefficient > 0.7) [15].

2.4. Determination of endothelial function

Ultrasound assessment of brachial artery flow mediated dilation (FMD) was performed on the right arm using a Logiq e ultrasound system (GE Healthcare Biosciences, Pittsburgh, PA) equipped with a 12 MHz linear array transducer. Brachial artery B-mode cine loops of 5 s were obtained in the longitudinal plane proximal to the elbow in the following order. First, a baseline cine loop was