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Cold-induced alteration of adipokine profile in humans

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Abstract

Adipose tissue function and sympathetic nervous system (SNS) activity are tightly interconnected. Adipose tissue is densely innervated by the SNS. Adipokines secreted by adipose tissue are implicated in maintaining energy homeostasis, the control of blood pressure, immune system function, hemostasis, and atherosclerosis. Little is known about a direct effect of SNS activation on influencing adipose tissue endocrine function in humans. In 10 lean, healthy male volunteers, SNS was activated by whole-body exposure to cold for 2 hours; a group of 10 subjects served as controls. Vital parameters were evaluated, plasma adipokine levels were measured, and adipokine gene expression in subcutaneous abdominal adipose tissue was determined. Cold exposure caused an increase in cold sensation and a drop in body temperature and heart rate. Norepinephrine, but not epinephrine, plasma levels were elevated. Adiponectin plasma concentrations were acutely and significantly decreased. There was a trend of increased monocyte chemoattractant protein–1 plasma concentrations. Interleukin-6 and leptin levels increased and decreased, respectively, in both groups. Vascular endothelial growth factor plasma levels were unaffected. Subcutaneous adipokine gene expression was unchanged. Cold exposure caused SNS activation and differentially influenced adipokine secretion. Adiponectin levels were acutely reduced, whereas monocyte chemoattractant protein–1 concentrations tended to increase. No specific changes in leptin and IL-6 concentrations were detectable. The observed alterations appeared to be posttranscriptional because adipokine gene expression was found to be unaltered.

1. Introduction

Adipose tissue function has a key role in maintaining energy homeostasis, the control of blood pressure, immune system function, hemostasis, and atherosclerosis. Many of these functions are mediated by adipose-derived hormones referred to as *adipokines* [1]. Some adipokines are considered to be proinflammatory including interleukin-6 (IL-6) and monocyte chemoattractant protein–1 (MCP-1) or involved in angiogenesis like vascular endothelial growth factor (VEGF). Others are associated with favorable metabolic effects (eg, reduction of insulin resistance), such as adiponectin and leptin [2,3].

Adipose tissue is well integrated in whole-body energy homeostasis and receives numerous afferences; the sympathetic nervous system (SNS) is one of these [4]. Previous studies demonstrated sympathoadrenergic innervations of adipose tissue in rodents and humans [5-8]. Sympathetic pathways originating from several areas of the brain involved in the regulation of energy balance have been identified at least in rodents [9]. On the metabolic level, it is well known that catecholamines stimulate lipolysis [10,11]. Apart from this direct effect of catecholamines on adipose lipid metabolism, some studies have investigated the effect of the SNS and adipokine profile in humans. Applications of adrenergic agonists or cold exposure have been the preferred ways to mimic or induce SNS activation, respectively. Leptin and IL-6 are the most intensively investigated adipokines in humans. Acute sympathoexcitation by administration of β-agonists yielded conflicting results regarding IL-6 secretion. Isoprenaline caused an increase in IL-6 plasma concentra-

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tions [12-14], but not norepinephrine [14]. Furthermore, leptin is of particular interest regarding the adipose tissue–SNS crosstalk, as it increases SNS activity at least in animal models [15]. On the other hand, several studies reported a decrease in leptin concentrations upon acute sympathoexcitation in humans [12,16-18], hence, some authors have postulated an SNS-leptin feedback loop. Of note, not all studies in humans cited above reported a control group.

The mechanisms mediating SNS-induced alterations of adipokine secretion remain to be elucidated. In the current study, we investigated clinical, biochemical, and endocrine responses at the level of adipokine secretion and expression in response to cold-induced sympathoexcitation. Ten lean, healthy male volunteers were exposed to cold for 2 hours and compared with a control group of 10 subjects without exposure to cold. Norepinephrine, epinephrine, adiponectin, MCP-1, IL-6, leptin, and VEGF plasma levels were monitored. Subcutaneous adipokine gene expression was evaluated.

2. Materials/subjects and methods

2.1. Subjects

Ten healthy male volunteers were included in each group. All subjects had a normal body mass index, did not smoke, and were not taking any medications. Screening blood tests and physical examinations were all normal. Results of relevant laboratory findings are displayed in Table 1. Each volunteer was instructed to avoid any food and beverages containing alcohol or caffeine after 8:00 PM on the day preceding the experiment. All subjects gave their written informed consent to participate. The study was approved by the local ethics committee and was conducted according to the principles expressed in the Declaration of Helsinki.

Table 1
Clinical characteristics and laboratory parameters at baseline

	Stimulated group	Control group
Age (y)	24.8 ± 1.263	24.5 ± 0.934
Weight (kg)	83.54 ± 4.138	82.1 ± 3.443
Height (cm)	181.65 ± 2.639	182.05 ± 3.268
BMI (kg/m^2)	25.164 ± 0.648	24.675 ± 0.463
% Fat (%)	19.5 ± 1.419	20.1 ± 0.897
Waist circumference (cm)	83.07 ± 2.413	87.45 ± 1.667
Hip circumference (cm)	98.63 ± 2.146	99.55 ± 1.322
Waist to hip ratio	0.841 ± 0.0193	0.865 ± 0.00678
Glucose (mg/dL)	91.5 ± 1.945	96.7 ± 2.329
Insulin (mIU/L)	5.346 ± 0.815	5.389 ± 0.584
Cortisol (μg/dL)	10.138 ± 1.182	8.895 ± 1.214
CRP (mg/L)	0.578 ± 0.0909	0.878 ± 0.260
TC (mmol/L)	4.114 ± 0.272	4.319 ± 0.166
HDL-C (mmol/L)	1.471 ± 0.126	1.531 ± 0.0967
LDL-C (mmol/L)	2.29 ± 0.206	2.369 ± 0.133
TG (mmol/L)	0.886 ± 0.118	0.972 ± 0.136

Major anthropometric characteristics and laboratory parameters were determined at baseline. There were no significant differences between both groups. Data are means ± SEM. BMI indicates body mass index; CRP, C-reactive protein; TC. total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

2.2. Experimental setup and protocol

The study design is schematically presented in Fig. 1. Subjects arrived at the laboratory at 8:00 AM and were dressed in a whole-body cooling suit with flexible pipes (custom-made). All participants wore the suit, regardless of whether they were assigned to the stimulated (ie, cold-exposed) or control group. Both groups were independent, as they were constituted by different individuals. Tap water was used as cooling agent; a thermostat (RS Components, Mörfelden-Walldorf, Germany) was used to control temperature with a variance of ±0.1°C. An 18-gauge venous catheter (Becton Dickinson, Madrid, Spain) was inserted into an antecubital vein for subsequent blood sampling. Vital parameters and individual cold sensation were measured. Blood samples were drawn at different points of time (Fig. 1), and samples were centrifuged (4000 rpm at 4°C for 7 minutes) to obtain plasma. Subcutaneous adipose tissue biopsies were performed at baseline and after 120 minutes as described by Kolaczynski et al [19]. After local anesthesia of the sampling area in the lower abdominal quadrants (2% mepivacaine; AstraZenica, Wedel, Germany), a 1.8 × 80–mm needle (Pleurofix; B Braun, Melsungen, Germany) was used in fan-shaped technique to obtain tissue samples.

2.3. Measurements

Body fat percentage was measured with a bioelectrical impedance scale (Tanita BC-543; Innerscan, Sindelfingen, Germany). Body temperature was taken sublingually using a conventional thermometer (model ACT 2000+; Scheiber, Kreuzwertheim, Germany). Blood pressure and heart rate were monitored oscillometrically (OSZ 5 Digital Blood Pressure System; Welch Allyn, Jungingen, Germany). Subjects evaluated their cold sensation by using a numerical analog scale, with 1 and 10 resembling the most hot and cold sensations, respectively. Adipokine plasma levels were determined using the following kits according to the manufacturer's manuals: full-length adiponectin: Bio Cat Human Adiponectin ELISA Kit (Bio Cat, Heidelberg, Germany); leptin: Human Leptin RIA Kit (LINCO Research, St Charles, MO); IL-6 (high sensitivity), VEGF, and MCP-1 plasma concentrations: Quantikine Human ELISA Kits (R&D Systems, Nordenstadt, Germany). Catecholamines were determined by high-performance liquid chromatography and subsequent chemical detection at our local Department of Clinical Chemistry. Routine laboratory parameters were determined with standard techniques also at our local Department of Clinical Chemistry.

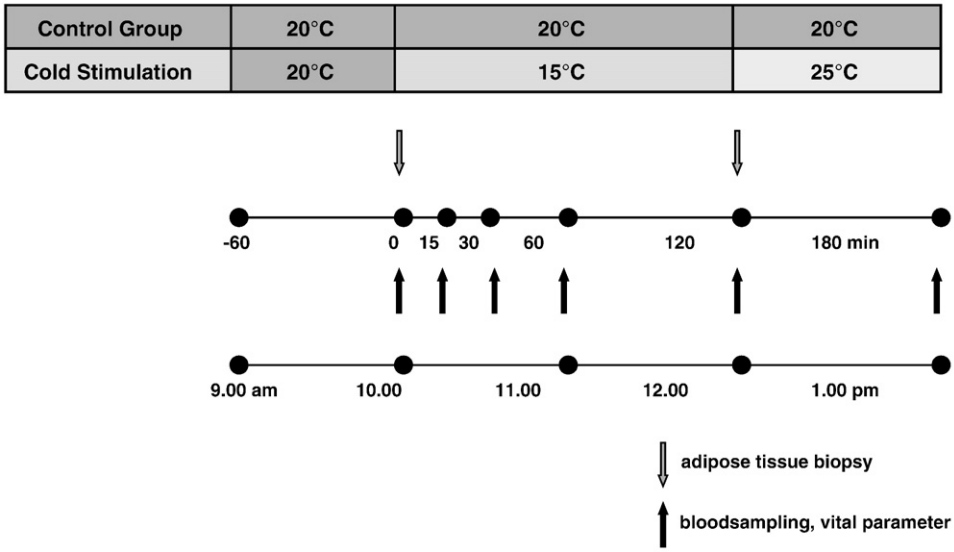

Fig. 1. Experimental setup. Experimental procedure started with a run in phase of 60 minutes. Acute sympathoexcitation was induced by cold exposure (15°C) for 120 minutes, followed by a warm-up period (25°C) for 60 minutes. Plasma samples were drawn; and vital signs were measured at baseline (0 minute) and after, 15, 30, 60, 120, and 180 minutes. Subcutaneous adipose tissue biopsies were performed at baseline and after 120 minutes. In the control group, the subjects were not exposed to cold; the remaining setup was identical. All subjects were studied in the morning.

2.4. RNA isolation and quantitative real-time reverse transferase polymerase chain reaction–based gene expression

Total RNA from adipose tissue samples was isolated by using the RNeasy Lipid Tissue Mini Kit (Qiagen; Hilden, Germany) according to the manufacturer's manual. Up to 1.65 μg total RNA was reverse transcribed using RT Superscript II (Invitrogen, Karlsruhe, Germany) and oligo dT primers (Roche Molecular Biochemicals, Mannheim, Germany) in the presence of RNase inhibitor (Roche Molecular Biochemicals). At least 2 μL of each reverse transferase reaction were amplified in a total reaction volume of 25 μL containing SYBR Green PCR Mix (Qiagen, Hilden, Germany). Primer sequences and temperature profiles for all target genes are available on request. The quantitative real-time reverse transferase polymerase chain reaction was performed using the ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City, CA, USA); hypoxanthine ribosyltransferase was used as housekeeping gene. Results are expressed relative to basal levels, defined as 100%.

2.5. Statistical analysis

Clinical characteristics, baseline laboratory parameters, and relative subcutaneous gene expression were analyzed by the Student *t* test. All other data were baseline-adjusted before analysis. All parameters were analyzed by a 2-way analysis of variance with "group" as between-subject factor and "time" as within-subject factor. When the analysis of variance yielded a significant effect, post hoc *t* tests were applied. Degrees of freedom were adjusted according to the Greenhouse-Geiser correction. *P* values < .05 were considered significant; those < .01, highly significant. SPSS 11.0 (SPSS Science, Chicago, IL) software was applied for statistical analysis. Given the sample size of n = 10 per group in the present study, effects of $d > 1.4$ can be revealed with a power of 84%.

3. Results

3.1. Clinical and laboratory parameters at baseline

Table 1 summarizes clinical and laboratory parameters associated with metabolic disorders. There were no significant differences between the stimulated and control groups.

3.2. Cold exposure reduces body temperature as well as heart rate and increases norepinephrine plasma concentrations

Cold exposure resulted in a statistically significant decrease in body temperature of 0.33°C (1%) after 180 minutes ($P < .01$) as compared with baseline. The difference between both groups was also statistically significant at 180 minutes ($P < .01$) (Fig. 2A). Individual sensation of cold, as determined by using a numerical analog scale, significantly increased by a maximum of 54% after 120 minutes ($P < .01$) and returned to basal level afterward. The differences between both groups were significant during cold exposure (Fig. 2B). During the experiment, temperature and cold sensation remained unchanged in the control group.

Heart rate acutely decreased by 6 beats per minute after 15 minutes (9%, $P < .01$) and reached a maximal reduction of 8 beats per minute after 180 minutes (14%, $P < .05$) with respect to baseline (Fig. 2C). There were no significant differences over time in the control group. Intergroup differences were significant starting at 15 minutes and reached a maximum at 180 minutes ($P < .01$). Systolic and diastolic blood pressure tended to increase in cold-exposed subjects

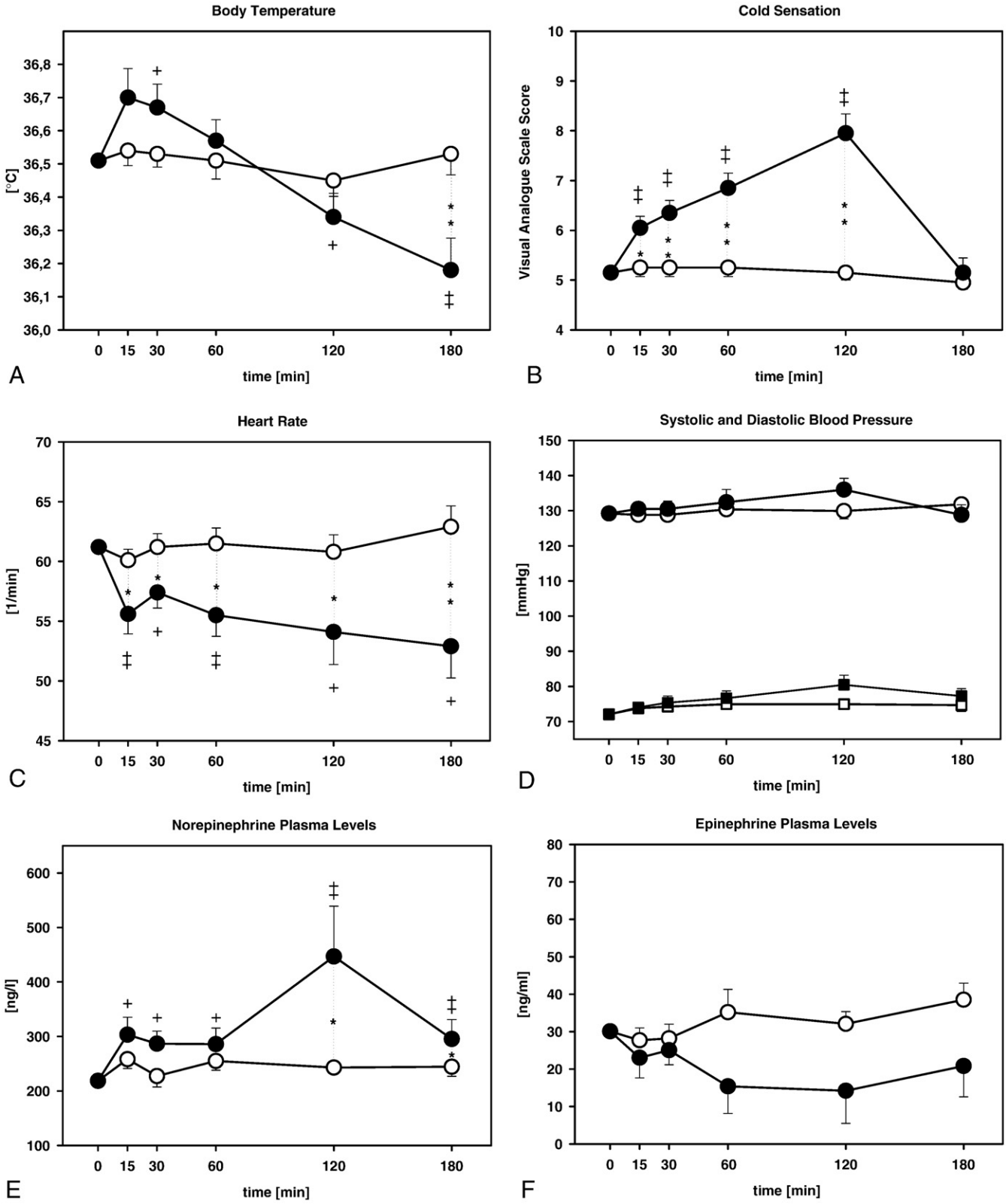

Fig. 2. Cold exposure effectively increases cold sensation, reduces heart rate, reduces body temperature, and increases norepinephrine plasma levels. Black symbols denote stimulated group; white symbols denote control group A, Body temperature. B, Individual sensation of cold as determined by a visual analog scale with 1 and 10 resembling the most hot and cold sensations, respectively. C, Heart rate. D, Systolic (circles) and diastolic (squares) blood pressure. E, Norepinephrine plasma concentrations. F, Epinephrine plasma concentrations. *$P < .05$ and **$P < .01$ between both groups at the same point of time. $^{+}P < .05$ and $^{‡}P < .01$ within one group at a specific point of time as compared with baseline. Data are means ± SEM.

over time, reaching a maximal difference after 120 minutes of 6.1 and 5.5 mm Hg, respectively; however, these intergroup differences were statistically not significant (Fig. 2D).

As shown in Fig. 2E, cold exposure caused a maximal 100% elevation of norepinephrine after 120 minutes ($P < .01$) as compared with the basal level. With respect to the control group, the difference was also significant at this point of time. A change of norepinephrine concentrations was not seen in the control group. By contrast, alterations of epinephrine concentrations did not reach statistical significance (Fig. 2F).

3.3. Sympathoexcitation alters adipokine plasma concentrations

Upon cold exposure, plasma leptin levels decreased, with a maximal reduction of 18% after 180 minutes. Leptin levels also declined in the control group during the experiment. A 15% reduction was detectable after 180 minutes. However, there were no differences between both groups (Fig. 3A).

Interleukin-6 plasma concentrations increased during the experimental procedure in both groups. Individuals exposed to cold showed a maximal increase of 400% after 180 minutes. A similar effect was also observed in control subjects with respect to baseline; it reached its maximum after 120 minutes (340%). Although the increase was less pronounced in the control group, there were no significant differences between both groups (Fig. 3B).

Plasma levels of adiponectin were acutely reduced by 16% after 60 minutes ($P < .05$) in response to cold-induced sympathoexcitation (Fig. 3C). Differences between the groups were significant at 30 ($P < .01$), 60 ($P < .01$), and 180 ($P < .05$) minutes.

Plasma MCP-1 levels tended to be higher in the stimulated group compared with both basal concentrations and control group, but these changes did not reach statistical significance (Fig. 3D).

Vascular endothelial growth factor plasma levels did not change between groups as well as over time (Fig. 3E).

Subcutaneous tissue messenger RNA concentrations of all the above-mentioned adipokines were determined before cold exposure and after 120 minutes. There were no significant changes in gene expressions (Fig. 3A-E, inserts).

4. Discussion

Acute cold exposure of humans caused a significant increase in norepinephrine concentration and a reduction in heart rate. Adiponectin plasma levels decreased and MCP-1 plasma concentrations tended to increase, whereas leptin, IL-6, and VEGF levels were not specifically altered. Changes were not correlated with gene expression patterns in subcutaneous abdominal adipose tissue at 120 minutes after cold exposure.

Few reports on SNS activation and subsequent changes of adipokine profiles in humans have been published. Considering the pleiotropic endocrine biology of this tissue, we investigated the acute effect on the regulation of important adipokines. Two major ways have been used to study acute effects of sympathoexcitation in vivo: (1) intravenous application of adrenergic agonists including epinephrine, norepinephrine, or isoprenaline and (2) cold exposure. Both approaches have obvious advantages and disadvantages. The SNS is known for its regional differences of innervation and activity. Increased sympathetic nerve activity, for example, in white adipose tissue, would cause a local increase of the primary postganglionic neurotransmitter norepinephrine. Plasma norepinephrine levels would only increase if there is a spillover into the circulation upon sympathoexcitation [5,20,21]. It is unclear whether systemic administration of adrenergic agonists is associated with adequate local concentrations and hence effects. On the other hand, cold exposure increases global SNS activity, resulting in increased plasma norepinephrine, but not epinephrine, concentrations [5,20,21]. Cold exposure can cause effects of its own, not easily distinguishable from direct consequences of sympathoexcitation.

For the current study, we chose cold exposure as a physiologic maneuver to activate the SNS using a whole-body suit for cooling. A strong and continuous increase in individual cold sensation and a significant decline in body temperature were detectable. The fall of the heart rate is also seen in other studies [22], which can be interpreted as baroreflexive reduction of cardiac sympathetic activity, although the accompanying increase in blood pressure did not reach statistical significance in our present study. Decreases in heart rate and increases in blood pressure are considered to be indicative of enhanced sympathetic activity to the vascular bed in response to cold, albeit the magnitude of changes in these hemodynamic parameters depends on the mode of cold exposure [23]. Plasma levels of norepinephrine, but not of epinephrine, rose 2-fold. This pattern of catecholamine concentrations is also typical for cold-induced SNS stimulation [17]. In fact, the adrenal medulla—and hence epinephrine levels—seems to be nonresponsive to cold exposure [24]. Changes of these parameters indicate excitation of postsynaptic noradrenergic sympathetic nerves without significant concomitant sympathomedullary activation in our present study. Despite a normalization of cold sensation due to the termination of the dermal stimulus, body temperature significantly decreased further during the "rewarming period." Norepinephrine plasma concentrations and heart rate also remained significantly elevated and reduced, respectively, in the stimulated group as compared with controls. The duration of SNS activation apparently exceeded the period of cold exposure.

Inhibition of subcutaneous blood flow in response to cold exposure could influence the plasma concentrations of adipokines secreted by subcutaneous adipose tissue. However, the different patterns of leptin, IL-6, and VEGF plasma levels particularly argue against a significant systemic effect. A decrease in plasma levels of all 3 adipokines should have

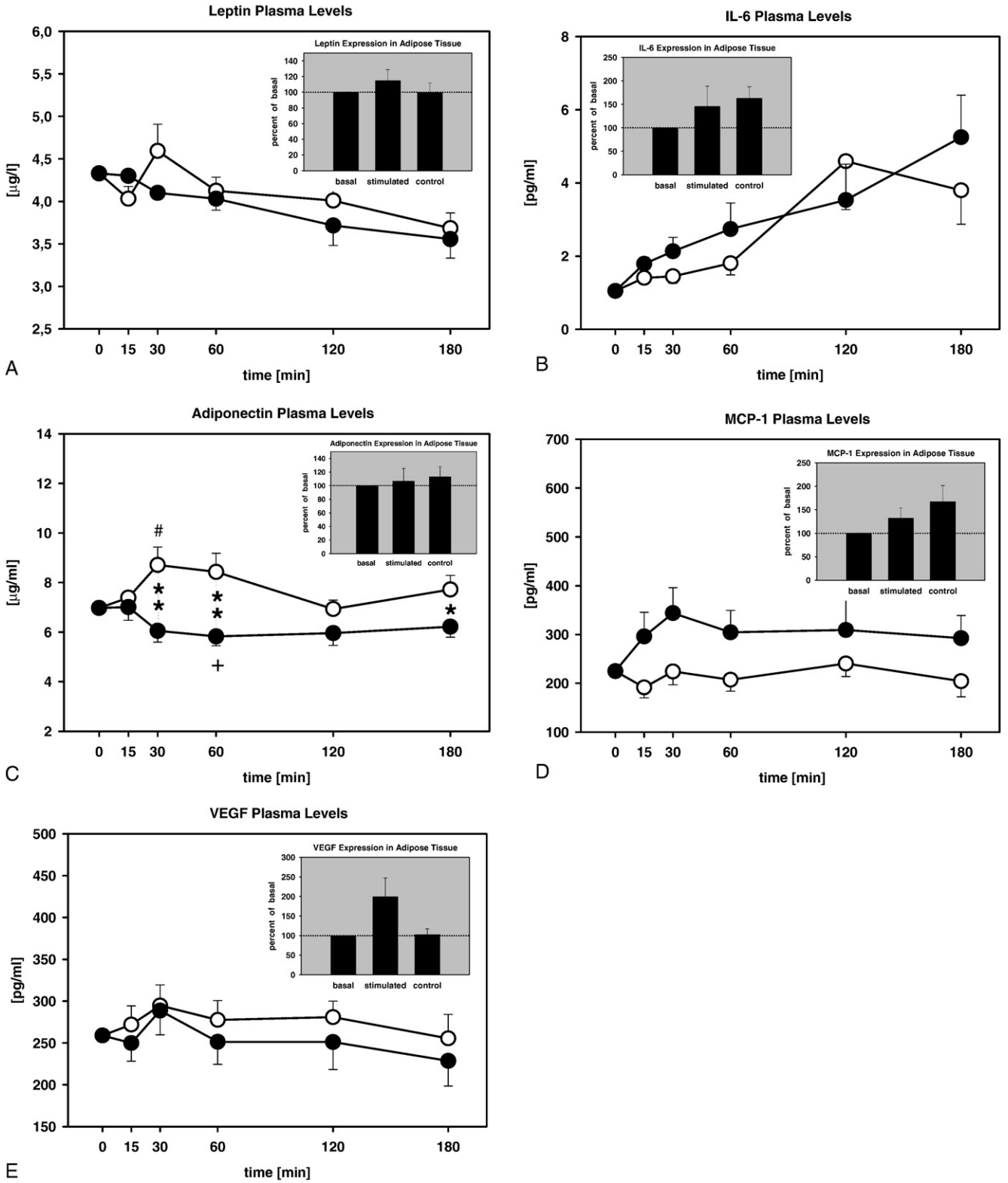

Fig. 3. Cold-induced sympathoexcitation reduces adiponectin secretion. Black circles denote stimulated group; white circles denote control group. Inserts denote messenger RNA levels in subcutaneous adipose tissue. A, Leptin plasma levels. B, IL-6 plasma concentrations. C, Adiponectin plasma levels. D, MCP-1 plasma concentrations. E, VEGF plasma levels. *$P < .05$ and **$P < .01$ between both groups at the same point of time. $^{+}P < .05$ within one group at a specific point of time as compared with baseline. Data are means ± SEM.

been seen in the stimulated group. Furthermore, different responses in the stimulated and control groups should be expected; but these adipokines display corresponding patterns in both groups.

Of the currently known adipokines, acute sympathetic regulation of leptin secretion has been studied most extensively in humans. Cold exposure [17] and adrenergic agonists [12,16,18] have been applied. A negative acute effect of the SNS on leptin secretion was demonstrated in vivo. Of these studies, only Donahoo et al [18] reported a control group; in this group, there was a downward trend of leptin levels that did not reach statistical significance. Our present study also shows a decrease of leptin plasma levels in both the simulated and control groups, without significant differences between both conditions. Thus, our data do not confirm a specific and acute effect of cold-induced SNS activation on leptin plasma concentration.

Results of previous studies examining IL-6 plasma levels in vivo upon acute adrenergic stimulation are conflicting. Isoprenaline increases IL-6 concentrations in some reports [12-14], whereas application of norepinephrine did not alter IL-6 levels [14]. The increase of IL-6 plasma levels in our experiment should be considered nonspecific, as it occurred in both groups. In fact, several studies have reported that simply the presence of an indwelling catheter can increase IL-6 values [25,26].

Obesity is associated with elevated levels of MCP-1, expressed and secreted by adipocytes, which lead to adipose tissue infiltration by macrophages [27]. To our knowledge, there are no reports on the acute effect of sympathoexcitation on MCP-1 levels in humans. It is tempting to postulate a proinflammatory effect of sympathoexcitation. The observed increase in MCP-1 plasma levels did not reach the level of statistical significance, but the power of our study is not sufficient to exclude an effect. This observation deserves further investigation.

Adiponectin is highly and specifically expressed in differentiated adipocytes [28], and plasma levels are negatively correlated with obesity and insulin resistance in humans [1]. It enhances insulin sensitivity in mouse models both for obesity and lipodystrophy [29], normalizes lipid abnormalities, and causes weight loss in mice with diet-induced insulin-resistance [30]. Several lines of evidence indicate an anti-inflammatory and antiatherogenic role of adiponectin [31]. One study demonstrated an association of high adiponectin levels with a metabolically healthy phenotype in obese patients, further indicating the positive effects of this adipokine in humans [32]. Our current study is the first to demonstrate a direct negative effect of cold-induced acute SNS activation on adiponectin regulation in humans. We did not see changes in adiponectin gene expression after 2 hours of cold exposure; hence, the effect on plasma levels appeared to be posttranscriptional. In fact, this effect appears to be acute but not sustained. Wijers et al reported on individual thermogenic responses to mild cold exposure (16°C) for 84 hours in a respiratory chamber. In healthy lean men, norepinephrine, but not epinephrine, levels increased after this prolonged cold exposure, whereas adiponectin levels remained unchanged. These findings are in line with an acute nature of a cold-induced adiponectin decrease independent of gene expression. Determining the physiologic consequence of this observation is beyond the scope of our study. However, it is known that adiponectin reduces blood glucose levels by inhibiting hepatic glucose output in mice [33]. Decreased glucose supply in case of an acute “fight or flight” situation would be unfavorable.

Further studies are needed to elucidate the pathophysiology of SNS and adipokines in patients with disorders like the metabolic syndrome. This syndrome, with obesity at the center, is characterized by a chronic inflammatory state and insulin resistance. There is growing evidence for an association of enhanced SNS activity and the metabolic syndrome as well as obesity [34-36].

Taken together, we provide evidence for a cold-induced sympathoexcitation and a change in the adipokine secretion profile. It is tempting to assume an acute negative effect of sympathoexcitation on adiponectin secretion. On the other hand, changes in leptin and Il-6 plasma levels were not specific; and our data do not support a previously assumed direct and specific effect of (cold-induced) sympathoexcitation. All changes are due to nongenomic alterations of adipokines secretion, although the precise mechanism remains to be determined.

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