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Increased sympathetic reactivity may predict insulin resistance: an 18-year follow-up study

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Abstract

Insulin resistance and sympathetic activity are related by a positive feedback system. However, which precedes the other still remains unclear. The present study aimed to investigate the predictive role of sympathoadrenal activity in the development of insulin resistance in an 18-year follow-up study. We also examined whether reactivity to 2 different stress tests, a cold pressor test and a mental stress test, would differ in their predictive power. The 2 tests are supposed to represent different reactivity mechanisms: α- and β-adrenergic responses, respectively. At entry, arterial plasma epinephrine and norepinephrine concentrations were measured in 99 healthy men (age, 19.3 ± 0.4 years, mean ± SD) during rest, a mental stress test, and a cold pressor test. Fasting plasma glucose concentration was measured at entry and at follow-up. Insulin resistance at follow-up was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR). Eighty subjects (81%) were eligible for follow-up after 18.0 ± 0.9 years (mean ± SD). The norepinephrine responses to cold pressor test at entry predicted plasma glucose concentration (r = 0.301, P = .010) and HOMA-IR (r = 0.383, P = .004) at follow-up in univariate analyses. In multiple regression analyses, corrected for fasting glucose at entry, family history of diabetes, blood pressure–lowering medication, body mass index at entry, and level of exercise, norepinephrine response to cold pressor test was found to be a positive predictor of future HOMA-IR (P = .010). This is the first long-term follow-up study in white subjects showing that sympathetic reactivity predicts future insulin resistance 18 years later. These findings may provide further insights into the pathophysiologic mechanisms of insulin resistance.

1. Introduction

Insulin resistance is one of the components of the metabolic syndrome and plays an important role in the pathogenesis of type 2 diabetes mellitus [1,2]. The well-documented association between insulin resistance and hypertension has been extensively studied and may represent a common regulating influence by the sympathetic nervous system [3-5]. It is well known that insulin resistance is related to sympathetic activity by a positive feedback mechanism, leading to their reciprocal reinforcement [6]. However, which of the 2 precedes the other still remains unclear. Landsberg [7] hypothesized that obesity was a primary factor and that excessive food intake would lead to hyperinsulinemia and overactivity of the sympathetic nervous system. Julius et al [3] postulated that changes in insulin sensitivity follow changes in muscle blood flow in hypertension based on an initially raised activity in the sympathetic nervous system. Later, Reaven et al [8] asserted that insulin resistance and hyperinsulinemia are the primary events, with subsequent enhancement of the sympathetic activity. Although there have been a large number of studies examining the relationship between sympathetic activity and insulin resistance, the cross-sectional design of the studies has made it difficult to solve the "chicken-and-egg" puzzle. To our knowledge, only 1 longitudinal study has so far been performed. This study demonstrated that the sympathetic activity seemed to precede hyperinsulinemia through a 10-year follow-up in Japanese subjects [9]. However, they did not examine insulin resistance.

The present study aimed to investigate the predictive role of sympathoadrenal activity in the development of insulin

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resistance in white subjects by means of fasting plasma glucose concentration and the homeostasis model assessment of insulin resistance (HOMA-IR), which is a marker of insulin resistance and has a close correlation with the insulin sensitivity index measured by the criterion standard euglycemic hyperinsulinemic glucose clamp [10]. We hypothesized that arterial plasma epinephrine and norepinephrine during rest and laboratory stress were related to fasting plasma glucose and HOMA-IR after 18 years of follow-up. We also examined whether reactivity to the 2 stress tests, a cold pressor test and a mental stress test, would differ in predictive power, as β-adrenergic responses predominate with mental stress and α-adrenergic with the cold pressor test [11,12].

2. Subjects and methods

The local ethics committee approved the study, and the procedures followed were in accordance with institutional guidelines. Written and informed consent was obtained from each subject at both the initial examination and follow-up.

2.1. Participants

All 19-year–old men in Norway have to attend a medical examination for the military draft procedure. Blood pressure (BP) measurements were undertaken by a trained physician once after 5 minutes of sitting by means of an automatic auscultatory device with a hidden printer (Boso-digital II S; Bosh & Sohn, Jungingen, Germany) or by using a newly calibrated mercury sphygmomanometer. None of the subjects were informed about the results of the BP recordings at this stage. Mean BP was calculated as diastolic BP + pulse pressure/3.

A total of 99 subjects were selected from the military draft screening, 30 belonging to the first percentile, 30 to the 50th percentile, and 39 to the 95th to 99th percentile of the mean BP distribution. This selection ensured that subjects from the whole BP range were represented, as resting BP is related to sympathoadrenal activity [13]. All were white except for one who was half-Asian and half-white. They were previously healthy without any history of diabetes, renal disease, elevated BP, or other cardiovascular disease and had normal results in physical examination, electrocardiogram, routine blood tests, and urinalysis. None was on medical treatment or abused drugs or alcohol.

2.2. Examination at entry

The protocol at baseline was described in detail elsewhere [12] and took place between October 1986 and October 1989. Resting heart rate and BP were recorded after 15 minutes at rest in a sitting position with the same equipment as during the screening. Height, weight, and waist circumference were measured standing. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. A short Teflon catheter (Venflon 19G; Viggo, Hälsingborg, Sweden) was introduced under local anesthesia without epinephrine (Xylocain; AstraZeneca, London, England) into the left brachial artery for blood sampling.

The cold pressor test lasted for 1 minute; and during that time, the right hand was completely immersed in ice water (0°C-4°C). During the mental arithmetic test, the subjects were asked to subtract the number “13” repetitively starting from “1079” for 5 minutes while a metronome made noise at a frequency of 2 Hz. They were informed about any miscalculation. After each test, there was a 30-minute recovery period. Arterial blood for catecholamine assay was collected after 30 minutes of supine rest; after 1/2 and 1 minute of the cold pressor test; and after 1, 3, and 5 minutes of the mental stress test. Catecholamine responses to stress tests were calculated as the mean value during stress subtracting the baseline value before the test. Blood was drawn in 10-mL glass tubes containing glutathione and ethylene glycol tetraacetic acid (EGTA), and plasma catecholamines were measured by radioenzymatic technique according to Peuler and Johnson [14] as previously reported [15,16]. All samples were analyzed by the same and blinded technician.

2.3. Examination at follow-up

Follow-up examinations were conducted from February 2005 to September 2006. Average time of follow-up was 18.0 ± 0.9 years. Eighty-one (82%) of the original 99 subjects were available for examinations. A total of 18 were not reexamined; that is, 1 was excluded because of probable intravenous drug addiction, 2 lived abroad and were not able to attend, 4 did not answer any letters or calls, and 11 did not want to participate. There were no significant differences in resting BP, heart rate, BMI, fasting plasma glucose concentration, or catecholamine stress responses between those who met for the follow-up and the others. One of the subjects who were reexamined had ulcerous colitis and was excluded from further analyses because of colectomy with instructions to ingest excess amounts of water and salt.

At follow-up, 21 subjects (25.9%) reported having one or more of the following diseases: hypertension (9 subjects), hypercholesterolemia (12), type 2 diabetes mellitus (3), and previous myocardial infarction (1). Eight of these subjects used one or more of the following medications regularly: angiotensin II receptor blockers (3), β-blockers (3), angiotensin-converting enzyme inhibitor (1), statins (2), oral antidiabetics (3), and acetylsalicylic acid (1).

Each subject was studied in the same room at 8.00 AM each day. They fasted and were instructed to abstain from any medication or smoking for the preceding 8 hours and from alcohol for the preceding 24 hours before the studies.

Resting BP was measured 3 times on the left arm after at least 15 minutes of sitting and was calculated as the mean of the last 2 measurements. Standardized questionnaires were used to collect information about concomitant diseases, medication, family history of diseases, education,

Table 1
Descriptives of the subjects at entry and after 18 years of follow-up

Characteristic	n	Entry	Follow-up
Age (y)	80	19.3 ± 0.4	37.3 ± 0.8
Systolic BP (mm Hg)	76	126 ± 20	131 ± 16*
Diastolic BP (mm Hg)	76	70 ± 17	89 ± 10**
Heart rate (beats/min)	75	66 ± 15	64 ± 12
BMI (kg/m^2)	80	22.4 ± 3.0	26.7 ± 4.3**
Waist circumference (cm)	34	83.0 ± 8.6	94.5 ± 11.1**
Triceps skinfold thickness (mm)	70	10.0 ± 4.2	12.2 ± 6.1**
Total serum cholesterol (mmol/L)	79	4.0 ± 0.7	4.9 ± 0.9**
Serum HDL cholesterol (mmol/L)	78	1.1 ± 0.2	1.2 ± 0.3
Serum triacylglycerols (mmol/L)	79	0.8 ± 0.4	1.3 ± 0.9**
Plasma glucose (mmol/L)	69	4.2 ± 0.5	5.1 ± 0.8**
Daily smokers (n [%])	78	28 (36)	20 (26)
Epinephrine during rest (pg/mL)	80	45.8 ± 31.4	
Epinephrine during MST (pg/mL)	67	116.1 ± 76.8	
Epinephrine response to MST (pg/mL)	65	75.9 ± 72.1	
Epinephrine during CPT (pg/mL)	74	78.5 ± 48.5	
Epinephrine response to CPT (pg/mL)	74	32.1 ± 45.3	
Norepinephrine during rest (pg/mL)	80	118.5 ± 56.7	
Norepinephrine during MST (pg/mL)	68	193.9 ± 78.1	
Norepinephrine response to MST (pg/mL)	66	76.1 ± 70.8	
Norepinephrine during CPT (pg/mL)	74	156.4 ± 75.3	
Norepinephrine response to CPT (pg/mL)	73	26.2 ± 60.8	

Data are presented as mean ± SD, except for daily smokers. Catecholamines represent arterial plasma concentrations. Catecholamine responses to stress tests were calculated as the mean value during stress subtracting the baseline value before the test. HDL indicates high-density lipoprotein; MST, mental stress test; CPT, cold pressor test.

* $P < .05$ vs entry, **$P < .001$ vs entry, using paired-samples t tests for normally distributed variables and Wilcoxon signed rank test when normality was not achieved by log-normal transformation. The proportions of smokers were compared using sign test.

occupation, and exercise. Baseline blood samples were drawn after a minimum of 30 minutes of supine rest.

The HOMA-IR was calculated in fasting conditions as serum glucose (in millimoles per liter) multiplied by serum insulin (in picomoles per liter) and divided by 135 as described by Matthews et al [10].

2.4. Statistics

The data were analyzed using the statistical package SPSS version 14.0 for Windows (SPSS, Chicago, IL). Parametric tests were used for normally distributed data, and nonparametric tests were used when normality was not achieved by log-normal transformation. The paired-samples t test was used to analyze changes in continuous variables, whereas the χ^2 test was used for categorical variables.

Associations were assessed using Pearson (r) or Spearman correlation (r_s). In the subsequent multiple regression analyses of future plasma glucose and HOMA-IR, the significant catecholamines from univariate analyses were included, in addition to fasting plasma glucose at entry, family history of diabetes mellitus, BP-lowering medication, BMI at entry, and level of exercise at the time of follow-up. Exercise was graded in 2 levels: less than 1 hour of exercise a week and more than or equal to 1 hour of moderate or heavy exercise a week.

3. Results

3.1. Descriptives

Characteristics of the participants at baseline and follow-up are presented in Table 1. Of the 99 persons included in the entry examination, 80 subjects (81%) were eligible for the follow-up analyses. They were on average 19.3 years old at the first visit (range, 18.2-20.8) and 37.3 years at the time of the reexamination (range, 35.4-38.9). Systolic BP ($P = .003$) and diastolic BP ($P < .001$) increased significantly, as did BMI, waist circumference, serum cholesterol, serum triglycerides, and fasting plasma glucose (all Ps < .001). Epinephrine and norepinephrine responses during the mental and cold pressor tests were highly significant ($P < .001$ for both tests).

3.2. Prediction of fasting plasma glucose and HOMA-IR at follow-up

The norepinephrine response to the cold pressor test at entry predicted plasma glucose concentration ($r_s = 0.301$, $P = .010$) and HOMA-IR ($r = 0.383$, $P = .004$) at follow-up in univariate analyses (Table 2). Fig. 1 illustrates the relationships according to quartiles of norepinephrine response to the cold pressor test. There were no significant associations with plasma catecholamines at rest or during mental stress.

In multiple regression analyses of follow-up glucose and HOMA-IR, the norepinephrine response to the cold pressor test was a positive predictor for future HOMA-IR, after correcting for fasting glucose at entry, family history of diabetes, BP-lowering medication, BMI at entry, and level of exercise ($\beta = .357$, $P = .010$, Table 3). Regarding fasting plasma glucose, the norepinephrine response to the cold

Table 2
Univariate correlations between levels of epinephrine and norepinephrine at entry and fasting plasma glucose and HOMA-IR at follow-up after 18 years

Catecholamine parameter at entry	Follow-up	
	Fasting plasma glucose[a]	HOMA-IR[b]
Rest		
E	−0.109	0.136
NE	0.055	−0.20
Mental stress test response		
E	−0.080	−0.144
NE	−0.117	−0.156
Cold pressor test response		
E	0.111	0.077
NE	0.301*	0.383*

E indicates epinephrine; NE, norepinephrine.

[a] Spearman correlations.

[b] Pearson correlations

* $P < .01$.

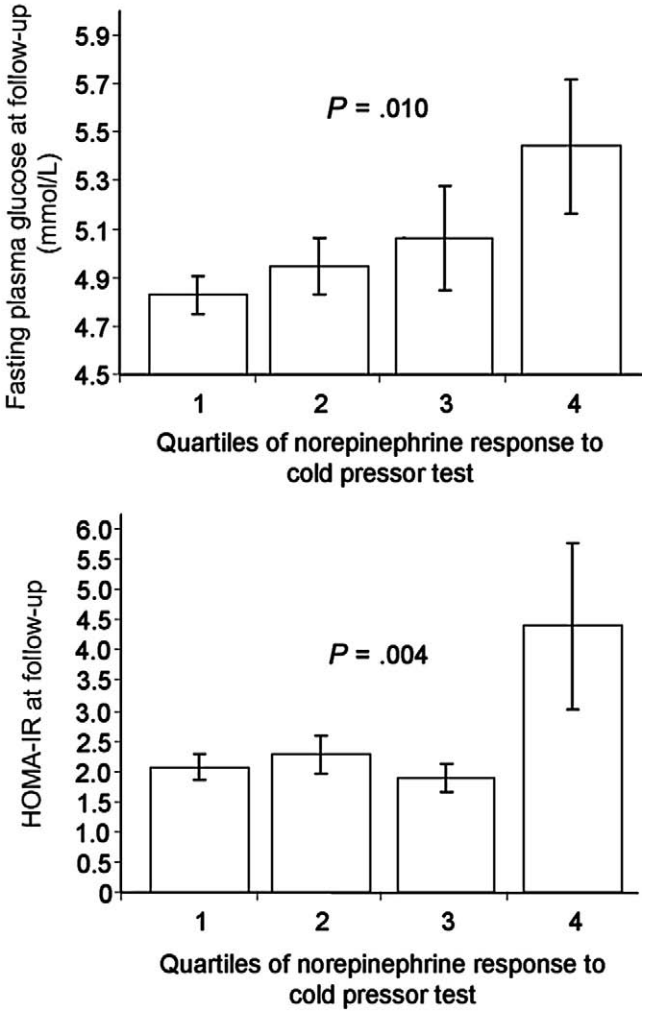

Fig. 1. Fasting plasma glucose and HOMA-IR after 18 years of follow-up (mean ± SEM) according to quartiles of norepinephrine response to the cold pressor test.

pressor test was no longer a significant predictor in this analysis. Furthermore, neither fasting plasma glucose at entry nor exercise level predicted any of the follow-up parameters of insulin resistance.

4. Discussion

The present study examined whether activities in the sympathoadrenal system during rest and 2 laboratory stressors were able to predict insulin resistance after 18 years of follow-up. We found that the norepinephrine response to the cold pressor test was positively related to fasting plasma glucose and HOMA-IR. This observation was confirmed by the multiple regression analyses, where the norepinephrine response was an independent positive predictor of HOMA-IR. As far as we know, this is the first study to demonstrate that increased sympathetic activity is related to future insulin resistance in white subjects in a follow-up study.

Confounding factors were eliminated to a minimum in the present study. All subjects were white men of the same age with no medication and with similar BMI at entry. As is generally the case in Norway, the population in Oslo is stable, reflecting genetic homogeneity. On the other hand, despite the advantage of a homogenous sample, this also implies a limited generalizability of the present results to other ethnicities, age groups, and women. Furthermore, we had no information on their diet.

Some would possibly argue that the 3 subjects with type 2 diabetes mellitus should be excluded from the analyses. However, they represent a true and important part of the blood glucose distribution in the population. Furthermore, as none of them took insulin, HOMA-IR is a suitable measure of insulin resistance in these subjects.

To assess sympathetic activity, we measured arterial catecholamines that previously were found superior than venous catecholamines to assess overall sympathetic activity [16]. It may be argued, however, that venous sampling could have been even more adequate and in fact increased the predictive power in the current setting because it better reflects norepinephrine spillover from skeletal muscle [17], especially during the cold pressor test [18]. This fact may also explain the somewhat modest, although highly significant, arterial norepinephrine response to the cold pressor test, in addition to the participants' young age [19] at entry and the inclusion of subjects with low BP.

Mancia et al [20] have argued that increased sympathetic activity may be the initial factor that induces insulin resistance and thus starts the cascade of events in the metabolic syndrome. Ward et al [21] (the Normative Aging Study) found that both plasma insulin levels and urine

Table 3
Multiple regression analyses of glucose and HOMA-IR at follow-up

Prediction of HOMA-IR at follow-up		
Model: adj. $R^2 = 0.370$, $P < .001$		
	β	P
Norepinephrine response to cold pressor test	0.357	.010
Family history of diabetes mellitus	0.203	.148
BP-lowering medication at follow-up	0.348	.022
BMI at entry	0.114	.400
Fasting plasma glucose at entry	−0.057	.648
Exercise, <1 h/wk (reference level)	–	–
Exercise, ≥1 h/wk	0.172	.188
Prediction of fasting plasma glucose at follow-up		
Model: adj. $R^2 = 0.189$, $P = .007$		
Norepinephrine response to cold pressor test	0.079	.525
Family history of diabetes mellitus	0.227	.087
BP-lowering medication at follow-up	0.226	.071
BMI at entry	0.231	.063
Fasting plasma glucose at entry	0.069	.569
Exercise, <1 h/wk (reference level)	–	–
Exercise, ≥1 h/wk	−0.052	.679

norepinephrine were independently related to hypertension. However, they stated that cross-sectional studies are not able to determine the cause-and-effect relationship between insulin resistance and sympathetic nervous system activity. Thus, longitudinal studies would be of value, particularly in a younger cohort of subjects. Our subjects were 19 years old at the time of entry and free of any diseases. The measurements at entry thus represent pure (patho)physiology without the bias from concomitant diseases or medications.

In the San Antonio Heart Study, tachycardia preceded development of diabetes; and the authors [22] discussed whether elevated plasma insulin levels were a cause of the increased sympathetic activity. Landsberg et al [7] believed that diet and obesity were key factors and suggested in their hypothesis that increased sympathetic nervous activity and plasma insulin elevation were secondary effects. Reaven et al [8] proposed that sympathetic activity was increased because of insulin resistance and hyperinsulinemia. Our findings are in line with the data presented by Masuo et al [9] suggesting that increased sympathetic activity is a predisposing factor for insulin resistance.

Whereas Masuo et al [9] measured venous plasma norepinephrine concentration in the resting state, we were able to analyze arterial plasma catecholamine concentrations during supine rest and stress separately and found that norepinephrine activity during the cold pressor test was the best predictor of future insulin resistance. Mental stress exerts its effects mainly through activation of β-receptors, whereas the cold pressor test on the other hand is considered as a noradrenergic test with stimulation of α-receptors [11,12]. The superiority of the cold pressor test in predicting future insulin resistance in the present study may be explained by an α-mediated reduced blood flow to skeletal muscles. Insulin resistance is inversely related to the number of open capillaries [23]; and our finding supports the hemodynamic hypothesis of Julius et al [3] stating that pressure-induced restriction of the microcirculation limits nutritional flow and thereby impairs glucose uptake in the skeletal muscle, which is the major site of insulin resistance [24]. Furthermore, a previous study found a direct relationship between the number of sympathetic neural bursts to skeletal muscle tissue and HOMA-IR [25].

A limitation of the study is the lack of fasting plasma insulin at entry. It is possible that those with greater sympathetic reactivity at baseline already had a higher level of insulin resistance. However, we included fasting plasma glucose in the multiple regression analyses, which has been shown to be an independent risk factor for type 2 diabetes mellitus in young men [26]. Likewise, it would be of interest to present arterial catecholamine measures at follow-up.

Other mechanisms than reduced blood flow to skeletal muscles may also explain the present data. Catecholamines have a direct effect on the insulin action (not the secretion), thereby inhibiting the glucose uptake [27]. Another possibility is that α-adrenergic vasoconstriction may contribute to raised hematocrit and whole-blood viscosity [28], thereby leading to increased peripheral vascular resistance and reduced nutritional flow [29,30].

In summary, we present the first longitudinal study assessing the relation between sympathoadrenal activity and future insulin resistance in white subjects. Sympathetic activity was a positive predictor of HOMA-IR after 18 years. These findings provide further insights into the pathophysiologic mechanisms of insulin resistance, suggesting that elevated sympathetic activity may be a predisposing factor for future insulin resistance.

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