Improved Insulin Sensitivity in 80 Nondiabetic Patients With MDD After Clinical Remission in a Double-Blind, Randomized Trial of Amitriptyline and Paroxetine

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Objective: There is substantial evidence that depression constitutes a risk factor for type 2 diabetes mellitus. A recent study has shown that high salivary cortisol levels are associated with decreased insulin sensitivity in unmedicated, depressed patients. Further, antidepressive treatment might have differential effects on hypothalamus-pituitary-adrenal (HPA) system activity. Therefore, the aim of the present study was to examine whether insulin sensitivity improves during antidepressive treatment in depressed patients with declining HPA system activity.

Method: Eighty inpatients with an episode of major depressive disorder (DSM-IV criteria) were treated in a double-blind, randomized protocol with either amitriptyline or paroxetine over a period of 5 weeks. After 6 drug-free days, an oral glucose tolerance test was performed on day 1 and again 35 days after antidepressive treatment. For quantification of free cortisol levels, saliva was obtained daily at 8:00 a.m. during weeks –1 (washout) and 5. The study was conducted from May 2005 to December 2005.

Results: The insulin sensitivity $index_{Matsuda}$ increased in only those patients who remitted from major depressive disorder as a result of treatment with either antidepressant ($F = 7.0$, $df = 1,74$; $p < .01$), while correcting for body mass index. Further, cortisol concentrations declined in remitters and responders to amitriptyline ($F = 2.1$, $df = 1,70$; $p < .05$), but not in any other subgroup.

Conclusion: Successful antidepressive treatment with either a selective serotonin reuptake inhibitor or a tricyclic substance increases the sensitivity to insulin in nondiabetic depressed patients. The herein presented longitudinal data do not exclude the HPA system as a major contributor to insulin resistance in depressed patients, but underscore the assumption of additional factors.

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There is substantial evidence that depression constitutes a risk factor for type 2 diabetes mellitus.[1,2] For decades, subtle disturbances in glucose metabolism have been described in depressed patients.[3–5] It may be assumed that both behavioral as well as biological factors contribute to the relationship between affective and metabolic disorders.[6] Recently, we found saliva cortisol in unmedicated, depressed patients to be negatively related to insulin sensitivity, as assessed by the oral glucose tolerance test (OGTT).[7] This finding supported the assumption that hypothalamus-pituitary-adrenal (HPA) system overactivity leads to glucose dysregulation in major depression and diabetes.[6]

Based on this observation, it may be hypothesized that antidepressant treatment that lowers HPA system activity might improve glycemic control, even independent from clinical response, while antidepressants without a dampening effect upon the HPA system should not.

So far, metabolic disturbances below the threshold of a clinical diagnosis of diabetes have not been the focus of research in depressed patients. However, antidepressant treatment of diabetic depressed patients has been shown to affect glycemic control. Both selective serotonin reuptake inhibitors (SSRIs)[8] and cognitive-behavioral therapy[9] have been shown to improve glycemic control in depressed diabetic patients. Even in nondepressed abdomi-

nally obese men, SSRI treatment may improve glucose tolerance.[10]

Basically, glucose utilization can be assessed using the euglycemic clamp technique or oral glucose tolerance testing. The euglycemic insulin clamp technique, as introduced by DeFronzo et al.,[11] is considered the gold standard to measure whole-body insulin sensitivity. However, the euglycemic clamp is not only expensive and time-consuming, but also difficult to perform in psychiatric patients who may not tolerate the discomfort of this examination. For follow-up studies in depressed patients, we preferred the OGTT. Various groups compared the validity of OGTT indices using the euglycemic clamp as the gold standard. Repeatedly, it was reported that the index derived by Matsuda and DeFronzo[12] is highly correlated to the euglycemic clamp ($r = 0.73$) and thereby, being superior to other indices derived from the OGTT, reflects complete body insulin sensitivity.[12,13]

Given that HPA system activation contributes to disturbed glycemic control,[7] changes in HPA system activity during the course of treatment should be relevant for metabolic disturbances. In our above-mentioned group of patients, we found saliva cortisol concentrations to decline in responders to amitriptyline, but not in nonresponders to amitriptyline or patients being treated with paroxetine.[14] Thus, we propose that the varying effects of tricyclic antidepressants and SSRIs on HPA system activity are again reflected in differing changes in insulin sensitivity. Taking this proposition into account, we increased our original database by not only incorporating follow-up OGTTs, but also by including additional patients within the same protocol in order to test the hypothesis that insulin sensitivity as measured by the OGTT would improve during antidepressive treatment in depressed patients with declining HPA system activity. The study was conducted from May 2005 to December 2005.

METHOD

Subjects

We included 80 inpatients with an episode of major depressive disorder according to DSM-IV, who scored at least 18 points on the Hamilton Rating Scale for Depression (HAM-D, 21-items) and completed a comparison of various biological outcome parameters between treatment with paroxetine or amitriptyline. Exclusion criteria were atypical depression, lifetime diagnosis of schizophrenia, bipolar disorder, and current substance-related disorders. The criteria of the American Diabetes Association[15] were used to diagnose type 2 diabetes (fasting glucose concentrations: > 6.9 mmol/L; 2-hour glucose concentrations: > 11.1 mmol/L), impaired fasting glucose (fasting glucose concentrations: 5.5–6.9 mmol/L), or abnormal glucose tolerance (2-hour glucose concentrations: 7.7–11.4 mmol/L). After complete description of the study to the subjects, written informed consent was obtained. Patients were treated with either amitriptyline (27 women/9 men; mean ± SD age: 51.0 ± 16.4 years; mean ± SD HAM-D score: 23.8 ± 4.7) or paroxetine (28 women/16 men; mean ± SD age: 58.2 ± 14.7 years; mean ± SD HAM-D score: 23.3 ± 3.5). None of the subjects received any antidiabetic or lipid-lowering medication and none were dieting.

Treatment

After a 1-week washout period, patients were treated with either amitriptyline 150 mg or paroxetine 40 mg for a period of 5 weeks. Medication was given double-blind randomized or according to clinical decision in separate subsets of patients. Throughout the study period, neither group was allowed other psychotropic medication except lorazepam and zolpidem. Patients with a HAM-D score of less than 18 after washout and dropouts are not included in this analysis. Treatment response was considered as a drop in HAM-D score of at least 50% during the active treatment phase, and remission was assumed when the final HAM-D score was below 7. Study design, as well as selection of patients, are thoroughly described in a recent article.[16]

Study Procedures

We studied oral glucose tolerance using a standard oral 75-g glucose loading on day 1 after a washout period of 6 days and again after 35 days of treatment. In brief, a 75-g glucose load was given at 10:00 a.m. after an overnight fast. Blood was sampled at baseline and 30, 60, 90, and 120 minutes after glucose ingestion using a catheter in an antecubital vein. Samples were immediately centrifuged and stored at –80°C for analysis of insulin and glucose. Each day, at 8:00 a.m., saliva was collected for the measurement of free cortisol. The mean saliva cortisol concentrations during week –1 (washout) and week 5 were used for further analysis.

Hormone Estimation

Clear saliva was used for duplicate analysis of cortisol using a time-resolved immunoassay with fluorescence detection. The lower limit of detection was 0.43 nmol/L with interassay coefficients of variation of less than 10%. Insulin was measured by a microparticle enzyme immunoassay (Abbott Laboratories, Tokyo, Japan). Intraassay variation for insulin was 5.2%; interassay variation was 6.2% at a mean concentration of 120 μU/mL. Glucose concentrations were determined by using the glucose-oxidase–derived technique, which showed an interassay variability of 3%.

Statistical Analysis

The OGTT results were used to calculate the insulin sensitivity index according to Matsuda and DeFronzo

($ISI_{Matsuda}$).[12] This index, established by the group that had also introduced the euglycemic clamp technique for assessing insulin sensitivity, is superior to other indices regarding its reflection of insulin sensitivity.[13] The whole-body insulin sensitivity index was calculated as follows: 10,000/square root of (fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT).

Multiple regression with body mass index (BMI) and saliva cortisol at baseline as independent and $ISI_{Matsuda}$ as dependent variables was used to assess the relationship between weight, HPA system activity, and insulin sensitivity. Repeated-measures analyses of variance (ANOVA-rm) with the factors "medication" (amitriptyline vs. paroxetine) and "response" (remission vs. response vs. nonresponse at day 35) as well as interaction effects were calculated to estimate their global effects upon the dependent variables, i.e., $ISI_{Matsuda}$, BMI, $ISI_{Matsuda}$ corrected for BMI, and saliva cortisol, as well as glucose and insulin, both under fasting conditions and 120 minutes after the glucose challenge. After determining these variables, we analyzed their local effects using 2-tailed Student t tests for paired samples.

Spearman correlation was applied to estimate the relation between HAM-D scores and glucose, insulin, and cortisol concentrations. Statistical significance was accepted at a p value of less than .05. Results are reported as mean ± SD.

RESULTS

According to the criteria of the American Diabetes Association, 42.5% of patients (N = 34) had normal glucose concentrations during OGTT, 6.2% of patients (N = 5) showed impaired fasting glucose concentrations, 31.2% of patients (N = 25) suffered from impaired glucose tolerance, and 20.0% of patients (N = 16) were found to have type 2 diabetes mellitus after the 6-day washout period.

Multiple regression confirmed BMI ($t = -2.98$; $p = .004$) and cortisol levels during washout ($t = -2.40$; $p = .02$) to explain 16% ($r = 0.40$) of the variance of $ISI_{Matsuda}$ before treatment. Thus, high pretreatment BMI and cortisol levels were negatively correlated with insulin sensitivity.

Regarding the course of BMI, ANOVA-rm showed strong effects of medication (amitriptyline vs. paroxetine; $F = 8.4$, $df = 1,74$; $p < .01$) and response status (remission vs. response vs. nonresponse; $F = 8.0$, $df = 1,74$; $p < .001$). This finding reflects increasing BMI in remitters only to amitriptyline and declining BMI in nonresponders to paroxetine (see Table 1).

ANOVA-rm showed a significant effect of repeated measures ($F = 7.0$, $df = 1,74$; $p < .01$) indicating a general increase of $ISI_{Matsuda}$ after treatment. The interaction effect, medication (amitriptyline vs. paroxetine) *remission (remission vs. response vs. nonremission), tended to affect the course of $ISI_{Matsuda}$ ($F = 2.5$, $df = 1,74$; $p < .09$). Further analyzing this effect using Student t tests, we found increasing insulin sensitivity in remitters, but not responders or nonremitters to both antidepressants.

Since BMI was related to $ISI_{Matsuda}$ ($r = 0.32$; $p < .01$), we wanted to exclude the possibility that the effects of remission were due to different effects of both drugs on BMI. Therefore, we performed an analysis of covariance (ANCOVA)-rm with the factors medication and response and BMI as covariate. This ANCOVA-rm confirmed a significant medication*response effect upon the course of $ISI_{Matsuda}$ ($F = 3.9$, $df = 2,148$; $p < .03$).

Regarding the effects of treatment upon glucose and insulin concentrations may help to interpret the changes of $ISI_{Matsuda}$ during treatment (see Figures 1 and 2). Response to treatment tended to be associated with lowered glucose concentrations after 120 minutes ($F = 3.0$, $df = 2,74$; $p < .06$). Similarly, but more pronounced, we found a significant effect of response on insulin concentrations at 120 minutes ($F = 5.5$, $df = 2,74$; $p < .02$). This effect reached statistical significance in remitters to amitriptyline and paroxetine, but not in other subgroups.

Regarding the course of mean morning cortisol concentrations in saliva, we found a significant effect of time ($F = 10.8$, $df = 1,70$; $p < .002$) as well as a significant effect of medication ($F = 2.1$, $df = 1,70$; $p < .05$). Using paired Student t tests, we confirmed declining cortisol concentrations in remitters and responders to amitriptyline, but not in any other subgroup.

Correlation analyses revealed a positive association between HAM-D scores after antidepressive treatment and OGTT concentrations of glucose at 120 minutes as well as insulin at 120 minutes ($r = 0.45$, $p < .001$ and $r = 0.39$, $p < .001$, respectively). $ISI_{Matsuda}$ correlated negatively with HAM-D scores after treatment ($r = -0.37$, $p < .001$). There was no relation between cortisol concentrations and HAM-D scores.

DISCUSSION

Depression is a common disorder, and the 2-fold increased risk for type 2 diabetes mellitus due to depression[1,2] is not only significant for a large group of individuals, but also for our health care systems. Recently, we found activation of the HPA system to be related to insulin resistance in depressed patients, especially in a subgroup of individuals with substantially increased saliva cortisol.[7]

The present longitudinal study is the first study to show improved glucose utilization after response to antidepressive treatment in nondiabetic depressed patients.

Thus, valid improvement of glucose utilization in depressed patients remitting during treatment with amitriptyline or paroxetine can be assumed. Throughout all parameters, the effects of clinical response were more

Table 1. Basic Characteristics of Inpatients With Major Depressive Disorder

	Amitriptyline (N = 36)			Paroxetine (N = 44)			Statistics		
Characteristic	Remitter (N = 16)	Responder (N = 11)	Nonresponder (N = 9)	Remitter (N = 17)	Responder (N = 7)	Nonresponder (N = 20)	F	df	p Value
Age, mean ± SD, y	54.9 ± 15.5	49.4 ± 18.0	46.0 ± 16.2	57.8 ± 13.3	52.4 ± 16.0	60.6 ± 15.5	F = 3.1[a]	1,68[a]	< .09[a]
Gender, female/male, N/N	14/2	5/6	8/1	11/6	2/5	15/5			
HAM-D score, mean ± SD									
Week –1	23.1 ± 5.2	26.5 ± 3.8	21.8 ± 3.8	22.3 ± 3.3	23.6 ± 2.1	24.0 ± 4.0			
Week 5	4.2 ± 1.7***	10.6 ± 2.8***	17.4 ± 3.8**	4.6 ± 1.7***	10.0 ± 0.8***	18.7 ± 5.9***			
BMI, mean ± SD							F = 8.4[a]	1,74[a]	< .01[a]
							F = 8.0[b]	1,74[b]	< .001[b]
Week –1	25.9 ± 5.3	25.5 ± 3.2	29.3 ± 7.6	26.5 ± 6.0	26.5 ± 2.3	27.7 ± 4.8			
Week 5	26.5 ± 5.3***	25.6 ± 3.2	29.1 ± 6.9	26.4 ± 5.8	26.3 ± 2.2	27.0 ± 4.4**			
Fasting glucose, mean ± SD, nmol/L									
Week –1	5.6 ± 0.9	5.2 ± 0.7	5.8 ± 1.5	5.6 ± 1.1	5.3 ± 0.2	5.9 ± 1.5			
Week 5	5.2 ± 0.8*	5.3 ± 0.9	5.9 ± 1.3	5.8 ± 1.6	4.9 ± 0.2**	5.6 ± 1.0			
Glucose 120 min,							F = 3.0[b]	2,74[b]	< .06[b]
mean ± SD, nmol/L							F = 2.5[c]	2,74[c]	< .09[c]
Week –1	8.0 ± 2.6	6.8 ± 2.1	9.3 ± 2.8	9.1 ± 3.8	6.9 ± 1.2	10.0 ± 4.3			
Week 5	6.4 ± 1.7***	6.9 ± 1.5	10.2 ± 3.9	8.0 ± 4.9	7.0 ± 1.1	8.8 ± 3.2**			
Fasting insulin, mean ± SD, pmol/L									
Week –1	128 ± 171	64 ± 18	89 ± 41	90 ± 52	74 ± 41	80 ± 38			
Week 5	68 ± 44	78 ± 43	84 ± 34	65 ± 30**	61 ± 36	87 ± 51			
Insulin 120 min,							F = 5.5[b]	2,74[b]	< .02[b]
mean ± SD, pmol/L									
Week –1	568 ± 584	507 ± 431	515 ± 312	566 ± 310	491 ± 515	670 ± 591			
Week 5	281 ± 204**	273 ± 138	576 ± 559	347 ± 197***	481 ± 408	609 ± 469			
$ISI_{Matsuda}$, mean ± SD							F = 7.0[d]	1,74[d]	< .01[d]
							F = 2.5[c]	1,74[c]	< .09[c]
Week –1	9.3 ± 5.4	10.3 ± 3.9	8.3 ± 5.5	8.5 ± 6.3	10.4 ± 5.5	8.3 ± 5.4			
Week 5	14.2 ± 7.7**	10.3 ± 3.2	7.2 ± 3.3	10.6 ± 5.4**	14.3 ± 11.6	9.9 ± 10.6			
Cortisol, 8:00 am,							F = 10.8[d]	1,70[d]	< .002[d]
mean ± SD							F = 2.1[a]	1,70[a]	< .05[a]
Week –1	28.0 ± 13.2	25.9 ± 9.9	27.7 ± 11.4	25.0 ± 10.0	22.2 ± 9.6	24.9 ± 11.6			
Week 5	18.7 ± 7.6**	15.9 ± 7.1**	28.0 ± 11.3	24.8 ± 11.4	19.6 ± 6.0	23.5 ± 8.7			

*p < .1.
**p < .05.
***p < .01.
[a]Statistic for ANOVA-rm with medication as factor.
[b]Statistic for ANOVA-rm with response as factor.
[c]Statistic for ANOVA-rm with medication*response as factor.
[d]Statistic for ANOVA-rm with time as factor.
Abbreviations: ANOVA-rm = repeated-measures analyses of variance, BMI = body mass index, HAM-D = Hamilton Rating Scale for Depression-21 item version, $ISI_{Matsuda}$ = insulin sensitivity index according to Matsuda and DeFronzo.[12]

pronounced than the effects of medication. Analyzing fasting and postchallenge insulin and glucose concentrations, the strongest effects were seen on postchallenge insulin in remitting patients, but no effects were seen in any other subgroup. This subgroup finding may underscore that improved insulin sensitivity is restricted to remitting patients.

From the clinical perspective, it is noteworthy that only remitting patients showed improvements in glycemic control. Of course, the nature of our data does not allow us to exclude the possibility that patients responding to antidepressant treatment might improve within the near future. Notably, patients responding but not remitting during treatment with paroxetine showed considerable, although not significant, increased insulin sensitivity. Physical activity is a major contributor to insulin sensitivity, even independent from weight change. Therefore, it could be speculated that the improved glycemic control in remitting patients is due to increased physical activity, which, regrettably, was not controlled in this study. However, the continued insulin resistance in subjects responding to treatment does not favor this assumption.

Insulin sensitivity improved significantly in remitters to treatment with amitriptyline. This may well be due to the lowering effect of amitriptyline upon HPA system activity.[14] Glucocorticoids mobilize substrates for liver gluconeogenesis, stimulate expression of gluconeogenic enzymes[17] as well as glycogen synthase, inhibit peripheral glucose uptake and utilization,[18] and stimulate lipolysis.[19] While these direct effects of glucocorticoids on energy metabolism may fade within days or weeks after attenua-

Figure 1. Insulin Concentrations During Oral Glucose Tolerance Test at Baseline and After Antidepressive Treatment

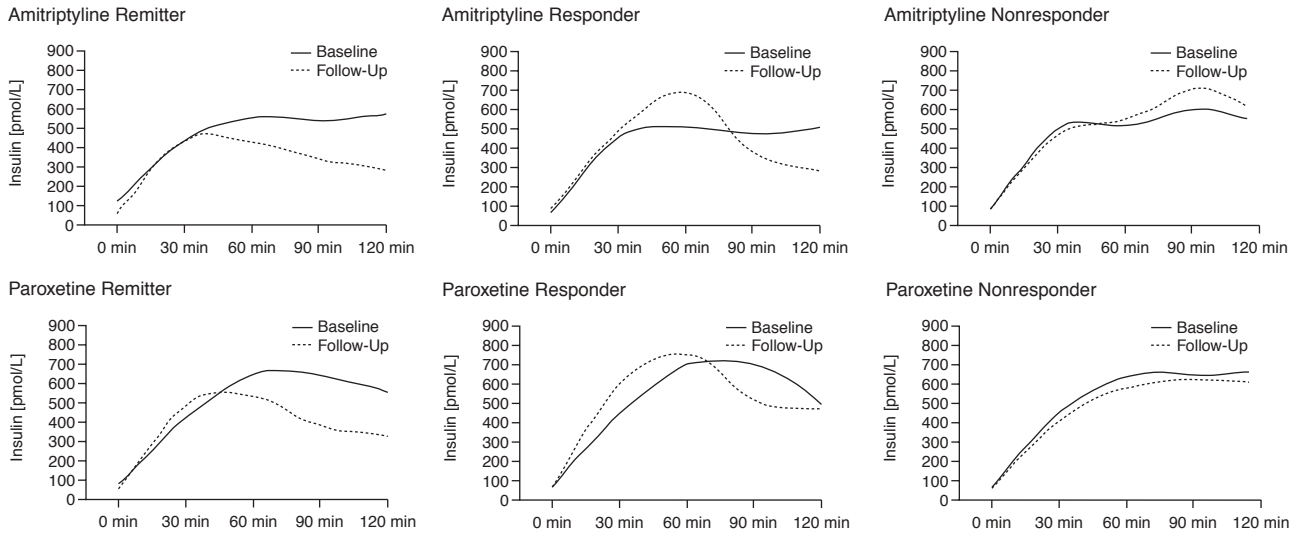
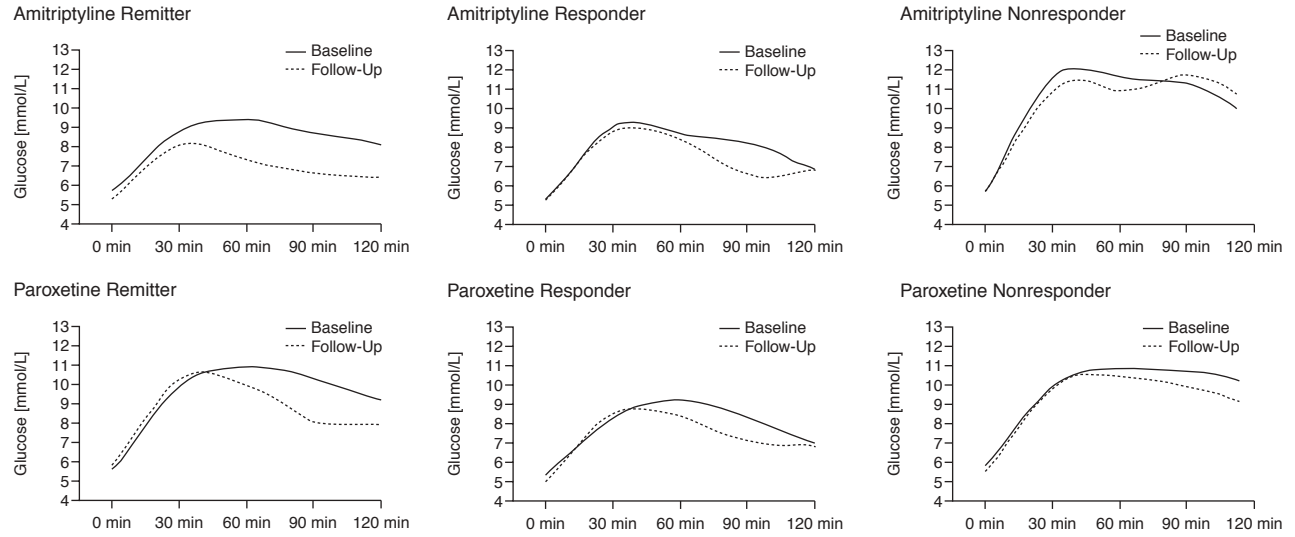


Figure 2. Glucose Concentrations During Oral Glucose Tolerance Test at Baseline and After Antidepressive Treatment



tion of HPA system activation, glucocorticoid-induced visceral obesity does not improve within short-term antidepressant treatment.[20,21] Clearly, the effects of antidepressants upon the HPA system cannot fully explain the changes of insulin sensitivity during the treatment period. First, responders to amitriptyline had reduced saliva cortisol concentrations after treatment, while insulin sensitivity did not change at all. Secondly, patients remitting to treatment with paroxetine had no changes in HPA system activity, while insulin sensitivity improved. Therefore, additional mechanisms must be operative that, finally, contribute to improved glucose utilization.

We hypothesize that serotonergic drugs may modulate peripheral energy metabolism and may induce changes of metabolism and appetite by means of central nervous effects and that effects upon the sympatho-vagal system may induce changes in insulin sensitivity. Regarding peripheral effects, the serotonin-2 (5-HT_2) receptor does not only play a role in the nervous system, but also in the intestines, platelets, and metabolism. Recently, we confirmed preclinical evidence that the 5-HT_2 receptor may be directly involved in the regulation of insulin sensitivity.[22] In fact, treatment with an SSRI substantially increases serum serotonin concentrations[23] and may in-

duce serotonergic effects in the muscle and thereby increase insulin sensitivity.[24] With respect to possible central nervous system–induced changes of metabolism, reduced central serotonergic responsivity, as assessed by fenfluramine testing, was found to be associated with the metabolic syndrome.[25,26] This may not only be due to the serotonergic modulation of appetite[27] but also to direct brain-mediated effects upon metabolism. The brain is increasingly regarded as a main regulator of energy homeostasis with adenosine triphosphate–sensitive potassium channels being involved in the sensing of energy and by inhibiting glucose uptake in muscle and adipocytes via the HPA system.[28] Specifically, hypothalamic sensing of glucose may contribute to lowering of hepatic gluconeogenesis via the vagus nerve.[29] Further, a decrease of insulin sensitivity can be caused by vagal denervation and is partially reversed by acetylcholine.[30] Thus, amitriptyline, as well as paroxetine, both being vagolytic at the level of autonomic regulation, may contribute to increased hepatic glucose production due to impaired vagal activity.[31]

The herein presented longitudinal data do not exclude the HPA system as a major contributor to insulin resistance in depressed patients, but underscore the assumption of additional factors. Glucocorticoid receptor antagonists, glucocorticoid synthesis inhibitors, or 11β hydroxysteroid dehydrogenase inhibitors would be the most feasible tools to test the specific role of HPA system activity for glycemic control in depressed patients.

Drug names: lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), zolpidem (Ambien).

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