Mode of Action of *Ipomoea Batatas* (Caiapo) in Type 2 Diabetic Patients

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We have previously reported the beneficial effects of Caiapo, the extract of white-skinned sweet potato (*ipomoea batatas*), on fasting plasma glucose, as well as on total and low-density lipoprotein (LDL) cholesterol in type 2 diabetic patients. The present study aimed to describe the underlying mechanism responsible for the improvement in metabolic control following administration of Caiapo in those type 2 subjects. A total of 18 male patients (age = 58± 8 years, body mass index [BMI] = 27.7 ± 2.7 kg/m^2, mean ± SEM) treated only by diet were randomized into 3 groups (placebo, low-dose Caiapo, 2 g/d, and high-dose, 4 g/d). Parameters related to glucose tolerance, glucose disappearance, and insulin secretion were obtained by performing both frequently sampled intravenous glucose tolerance test (FSIGT) and oral glucose tolerance test (OGTT) before and after 6 weeks of treatment with Caiapo. Following treatment with high dose Caiapo, insulin sensitivity significantly ameliorated when assessed both with OGTT (from 308 ± 13 mg/min/m^2 to 334 ± 10, $P = .048$) and FSIGT (from 1.21 ± 0.32 10^4 min^{-1}/(μU/mL) to 1.73 ± 0.40, $P = .021$). Improvement of insulin sensitivity with the low dose was observed only with the FSIGT (from 2.02 ± 0.70 10^4 min^{-1}/(μU/mL) to 2.76 ± 0.89, $P < .05$). Glucose effectiveness did not change. While no changes in glucose tolerance were observed in the placebo and low-dose groups, it increased from 0.85 ± 0.13 %min^{-1} to 1.46 ± 0.13 ($P < .02$) in patients on high dose. No significant changes were seen in any of the parameters related to insulin dynamics: insulin secretion (from C-peptide), distribution, clearance, and hepatic extraction remained virtually the same after the treatment. In conclusion, short-term treatment with 4 g/d of the nutraceutical Caiapo consistently improved metabolic control in type 2 diabetic patients by decreasing insulin resistance without affecting body weight, glucose effectiveness, or insulin dynamics. No side effects related to the treatment were observed. Thus these results indicate that Caiapo could potentially play a role in the treatment of type 2 diabetes.

THE PATHOGENESIS of type 2 diabetes involves insulin resistance, increased hepatic glucose output, and impaired insulin secretion.[1,2] These features are potential targets for pharmacologic intervention in addition to diet and increased physical activity.[3] Recently, it has been conclusively shown that appropriate metabolic control in type 2 diabetes is of major importance for the prevention of diabetic complications.[4] In addition to drugs, which act on insulin secretion, hepatic glucose output and intestinal absorption, new compounds that improve insulin sensitivity are currently under investigation or already in clinical use.[5-7] Potential side effects of these medications, such as hypoglycemia or weight gain,[4] cause an increasing number of patients to use herbs or nutraceutical products for the treatment of diabetes.[8]

We have recently shown the effect of the extract of white-skinned sweet potato (*ipomoea batatas*) on reducing fasting plasma glucose, total, and low-density lipoprotein (LDL) cholesterol in type 2 diabetic patients.[9] That study also showed that this extract, called Caiapo, reduces insulin resistance if administered in a high dose. In the present report, we describe in detail the underlying mechanism responsible for the improvement of glucose control following administration of Caiapo in those type 2 subjects. Parameters related to glucose tolerance, glucose disappearance, and insulin secretion were obtained by performing both intravenous and oral glucose tolerance tests.

MATERIALS AND METHODS

Patients and Study

A total of 18 male type 2 diabetic patients (58 ± 8 years, body mass index [BMI] 27.7 ± 2.7 kg/m^2, blood pressure 139 ± 17 mm Hg, glycosylated hemoglobin [HbA_{1c}] 7.1% ± 0.3%) participated in this study. They were treated only by diet and were not taking any other type of drug known to affect glucose metabolism. Basal glucose and insulin were 151 ± 7 mg/dL (8.4 ± 0.4 mmol/L) and 10.1 ± 1.9 μU/mL (60 ± 12 pmol/L), respectively. The study was prospective, placebo controlled, randomized, and double blind. Patients were randomized (6 per group) to receive for 6 weeks 4 tablets a day containing either placebo or 168 mg (low dose) or 336 mg (high dose) each of powdered white sweet skinned potato (*Ipomoea batatas*) cortex, before breakfast, lunch, and dinner for a total of 2 or 4 g/d Caiapo. Basal characteristics of the placebo group were: age 57 ± 3 years and BMI 28.9 ± 0.9 kg/m^2; low-dose group: 59 ± 2 and 25.8 ± 0.8; high-dose group: 57 ± 5 and 28.6 ± 1.3, respectively. The Ethics Committee of the University of Vienna approved the study protocol, and informed consent was obtained from all patients prior to inclusion into the study. Each subject underwent an oral glucose tolerance test (OGTT) and a frequently sampled intravenous glucose tolerance test (FSIGT) in randomized order before and after 6 weeks of Caiapo administration. At least a 2-day interval elapsed between the tests.

Tests and Data Analysis

FSIGT. Glucose was injected at a dose of 0.3 g/kg followed by an injection of insulin (0.05 U/kg) after 20 minutes. Blood samples were collected during 3 hours with frequent sampling during the first 30 minutes for the measurement of glucose and insulin concentrations. A list of calculated parameters with their meaning is reported in Table 1.

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Table 1. List and Meaning of Symbols and Abbreviations

Parameter	Meaning	Test
AIR_G	Glucose-stimulated acute insulin response	FSIGT
AUC_{CP}	Area under the C-peptide concentration curve	OGTT
AUC_G	Area under the glucose concentration curve	OGTT
AUC_I	Area under the insulin concentration curve	FSIGT, OGTT
BSR	Basal insulin secretion rate (from C-peptide)*	OGTT
Cl_I	Metabolic clearance rate of insulin	FSIGT
CP_b	Fasting level of C-peptide	OGTT
DI	Disposition index	FSIGT
GD	Disposition index	OGTT
HE	Total hepatic insulin extraction	OGTT
K_G	Glucose tolerance index	FSIGT
OGIS	Insulin sensitivity index	OGTT
S_G	Glucose effectiveness	FSIGT
S_I	Insulin sensitivity index	FSIGT
TIS	Total amount of secreted insulin (from C-peptide)*	OGTT

*Parameters of insulin secretion are expressed per unit distribution volume.

The glucose tolerance index K_G represents the rate of glucose disappearance and was calculated as the slope of the logarithm of plasma glucose concentrations versus time from 8 to 19 minutes. Changes in plasma insulin were described by the whole area under the curve of insulin concentration (AUC_I) that includes both the endogenous and the exogenous hormone. The endogenous response to glucose stimulation was described by ΔAIR_G, the average suprabasal insulin concentration in the interval 3 to 10 minutes. Insulin clearance (Cl_I) was calculated as the ratio between the insulin dose and the area under the concentration curve from 20 to 180 minutes.[10] FSIGT data were analyzed with the minimal model method[11] that yields the insulin sensitivity index (S_I): ie the ability of insulin to promote glucose disappearance; and glucose effectiveness (S_G): ie, the ability of glucose per se to promote its own disappearance without any increment in insulin.[12] The product $DI = S_I \times AIR_G$, termed disposition index (DI), represents an integrated picture of factors controlling glucose metabolism, ie, insulin sensitivity and secretion.[13]

OGTT. The standard dose of 75 g glucose in H_2O solution was administered. Venous blood samples were collected for insulin, C-peptide, and glucose measurements in the fasting state and at 10, 20, 30, 40, 60, 90, 120, 150, and 180 minutes after glucose load in the morning following an overnight fast. In addition to the areas under glucose (AUC_G), insulin (AUC_I), and C-peptide (AUC_{CP}) concentration curves, OGTT data were analyzed by mathematical models for assessing insulin secretion, appearance,[14,15] and insulin sensitivity. The secretion model reconstructs the patterns per unit volume of C-peptide β-cell release and posthepatic insulin appearance into peripheral circulation, providing a figure of the β-cell function and of insulin degradation in the liver. From the concomitant analysis of C-peptide and insulin data, the model allows the estimation of the basal fasting prehepatic insulin secretion rate per unit volume (BSR) of the stimulated insulin secretion per unit volume (TIS), ie, the total amount of insulin released by the β cell during the OGTT, and of the hepatic insulin extraction (HE) (as percent of the secreted hormone) during the whole test (not just the first pass). Insulin sensitivity from OGTT was calculated according to a recently proposed formula that was derived from a comprehensive mathematical model of glucose clearance after an oral administration.[16] This formula allows the calculation of glucose clearance that is an OGTT-based index of insulin sensitivity (OGIS). This has been validated against the corresponding value obtained during the gold standard glucose clamp and already used successfully in other studies.[17] The ability to dispose of glucose that relates insulin action to the prevailing insulin amount is given by the glucose disposal index, $GD = OGIS \times \Delta AUC_I$, where ΔAUC_I is the suprabasal component of the area under the insulin curve. GD is an extension to OGTT of DI of FSIGT and provides another quantitative figure of the overall metabolic status by simultaneously accounting for insulin action and secretion.

AUCs were calculated with the trapezoidal rule. Comparisons have been evaluated by the analysis of variance, paired, and unpaired *t* test where appropriate. Data and results are expressed as means ± SEM unless otherwise designated.

RESULTS

No adverse events were reported during the 6-week period of treatment. Body weight (BMI = 27.7 ± 1.1 kg/m^2) and blood pressure (130 ± 19 mm Hg) remained unchanged in the 3 groups, as well as basal insulin and C-peptide ($P > .2$). Basal glucose was reduced in the high-dose group from 150 ± 10 mg/dL to 130 ± 7 ($P = .049$), but did not change in the placebo or low-dose groups ($P > .26$).

FSIGT

Following high-dose Caiapo treatment, a reduction in plasma glucose concentration during the late phase of the FSIGT was observed (Fig 1, $P < .05$ at 150 minutes), whereas no change was seen in plasma insulin concentrations. The FSIGT analysis (Table 2) showed an increase of insulin sensitivity (S_I) by 37% in those receiving low-dose Caiapo, while no other parameter exhibited any change. High-dose Caiapo increased S_I by 42% and improved the overall glucose tolerance (K_G) by 72%. These improvements occurred in the face of unchanged dynamics of insulin, both in terms of secretion (given the similar concentrations during the early endogenous phase) and metabolic clearance rate. In fact, endogenous insulin, as assessed by the AUC_I and AIR_G during the first phase of the test: ie before insulin injection, was virtually the same in any group before and after Caiapo. The global DI accounting for the combined effects of insulin sensitivity and insulin secretion was also increased with high-dose treatment. Figure 2 shows that, despite the low number of subjects, the hyperbolic relationship between sensitivity and secretion is significantly ($P < .01$)

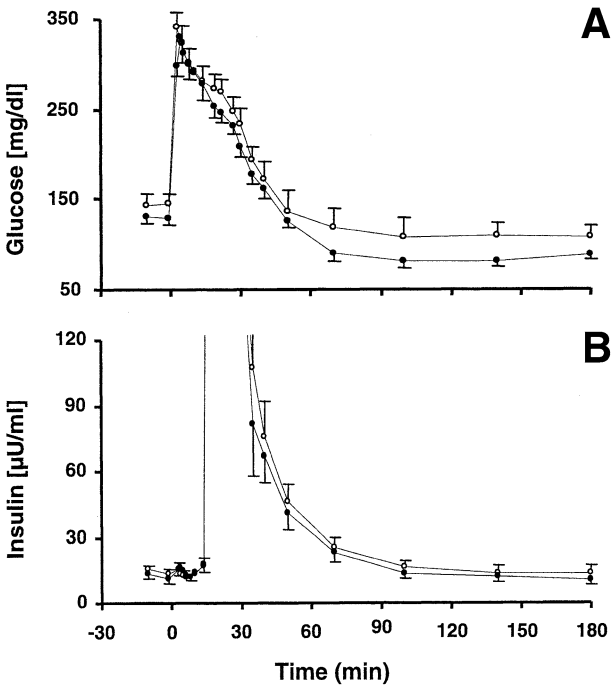

Fig 1. Plasma concentrations of (A) glucose and (B) insulin during FSIGT before (○) and after (●) treatment with high-dose Caiapo (mean ± SEM, N = 6). Glucose (0.3 g/kg) is injected at zero-time; insulin (0.05 U/kg) at 20 minutes. During the early phase, before insulin administration, glucose disappearance rate (see K_G, Table 2) was increased in the Caiapo group. The increased effect of insulin on glucose disappearance after Caiapo is observed throughout the test. No endogenous insulin response occurred in both groups before insulin administration. Peak values following exogenous insulin were 693 and 638 μU/mL before and after Caiapo, respectively. Insulin concentration levels were not different at any data point.

shifted to the right: ie, toward an amelioration of the overall glucose tolerance. Thus, we can summarize that despite similar prevailing insulin, plasma glucose disappeared faster in response to Caiapo, suggesting increased insulin action, because no difference was observed for S_G.

OGTT

Postload plasma concentrations of glucose were lower in subjects treated with high-dose Caiapo (Fig 3), who exhibited lower AUC_G and a 18% reduction of 2-hour glucose levels, while no significant differences with pretreatment were found for the other groups ($P > .35$). Table 3 shows measurements and parameters obtained from OGTT data. With high-dose treatment, OGIS was higher showing that the improvement in insulin sensitivity is observed also after a more physiologic oral glucose load. The measurements of C-peptide allowed a broader analysis of the effects of Caiapo on the glucose-stimulated insulin response. No appreciable difference ($P > .4$) was observed in CP_b and AUC_{CP}, meaning that the β cell is not affected by Caiapo, as also demonstrated by the modeling-analysis quantification of the basal (BSR) and dynamic (TIS) β-cell (prehepatic) activity, which were unchanged with Caiapo ($P > .2$). Peripheral insulin also was the same after treatment in any group, reflecting an unchanged handling of the hormone by the liver, as quantified by the measurement of HE ($P > .3$). The glucose disposal index GD that accounts for the interplay between insulin sensitivity and secretion was significantly increased with high-dose Caiapo. While no change was observed in the low-dose group ($P = .17$), a significant decrease of GD was detected in the placebo group showing a deterioration of glucose tolerance without Caiapo even in the short term. These OGTT results were in accordance with what was found for insulin secretion, clearance, sensitivity, and DI from FSIGT, and it is particularly interesting to observe that the 2 indexes of

Table 2. Metabolic Parameters From FSIGT Before (B) and After (A) Treatment With Placebo or Caiapo in the Single Groups (n = 6 for each group)

			Caiapo	
		Placebo	Low Dose	High Dose
K_G (% min^{-1})	B	0.92 ± 0.10	0.68 ± 0.12	0.85 ± 0.13
	A	1.04 ± 0.12	0.79 ± 0.12	1.46 ± 0.13*
S_I (10^4 min^{-1}/μU/mL)	B	1.52 ± 0.28	2.02 ± 0.70	1.21 ± 0.32
	A	1.35 ± 0.21	2.76 ± 0.89†	1.73 ± 0.40‡
S_G (min^{-1})	B	0.013 ± 0.001	0.011 ± 0.002	0.013 ± 0.001
	A	0.013 ± 0.002	0.014 ± 0.003	0.016 ± 0.002
AUC_I (min mU/mL) interval 0-10	B	0.12 ± 0.04	0.08 ± 0.02	0.14 ± 0.02
	A	0.12 ± 0.04	0.08 ± 0.02	0.14 ± 0.02
AUC_I (min mU/mL) interval 0-180	B	6.98 ± 1.31	7.38 ± 1.27	11.04 ± 1.96
	A	8.47 ± 0.80	7.14 ± 1.75	9.96 ± 1.85
AIR_G (μU/mL)	B	13.0 ± 4.4	8.0 ± 1.7	13.1 ± 2.1
	A	12.1 ± 4.1	7.8 ± 1.5	14.3 ± 2.5
Cl_I (mL · min^{-1} · kg^{-1})	B	10.8 ± 2.0	9.4 ± 1.3	7.2 ± 1.6
	A	7.3 ± 0.9	11.2 ± 2.1	6.5 ± 1.4
DI (10^{-2} min^{-1})	B	0.16 ± 0.02	0.13 ± 0.03	0.13 ± 0.03
	A	0.13 ± 0.02	0.17 ± 0.04	0.20 ± 0.02§

NOTE. See Table 1 for parameter meaning; n = 6 per group.
Compared with pretreatment: *$P < .02$; †$P < .05$; ‡$P = .021$; §$P < .01$.

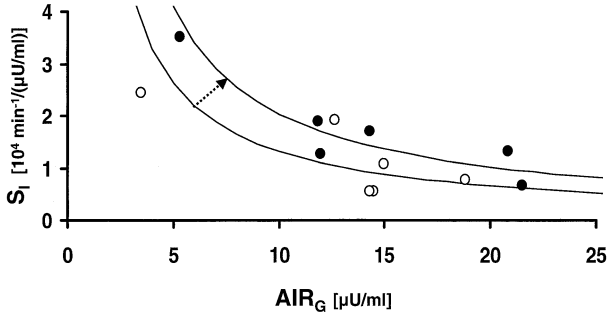

Fig 2. Hyperbolic relationships between insulin sensitivity and secretion before (○) and after (●) 6 weeks of high-dose Caiapo in 6 type 2 patients. The significant ($P < .01$) shift to the right of the curve after treatment (arrow) indicates the improvement induced by Caiapo treatment of the overall glucose disposal following the 0.3 g/kg of intravenous glucose load.

insulin sensitivity (OGIS from OGTT and S_I from FSIGT) were significantly correlated across the whole range ($r = .52$, $P = .001$, Fig 4).

DISCUSSION

This report follows a previous observation on the beneficial effects of 6 weeks high-dose Caiapo in lowering fasting plasma glucose, total, and LDL-cholesterol in type 2 diabetic subjects treated by diet alone.[9] It describes in detail insulin sensitivity and release obtained by mathematical model analysis of dynamic experiments, such as the oral and the intravenous glucose tests. Improvement of glucose tolerance after 6 weeks high-dose Caiapo was detected by the model-independent observation of the decreased AUC_G during the OGTT and of the increased K_G during the FSIGT. This improvement was demonstrated to be due to the amelioration of insulin sensitivity.

In general, improved glycemic control can be attributed to a number of different mechanisms, including reduced intestinal glucose absorption, increased insulin secretion and improved insulin sensitivity.[3] The glycemic profile during the OGTT argues against a delay in resorption, which should have led to a pronounced decrease of glucose levels during the first phase of the OGTT, which only occurred later during the test. A stimulatory effect on insulin secretion can be excluded by the unchanged AUC_I during OGTT and early phase of FSIGT. Our results clearly indicate that Caiapo exerts its beneficial effects via reducing insulin resistance, having observed an improvement of insulin sensitivity in both dynamic tests.

While with high-dose Caiapo, the improvement of glucose tolerance and insulin sensitivity was evident after both intravenous and oral glucose loads, with the low dose, the improvement was detected only with the S_I index of FSIGT, which was reflected only by a nonsignificant trend in the improvement of postload glucose excursion. The index S_I is indeed very robust[11] and able to detect even subtle differences, which are not so evident with other measurements on the data, such as, for instance, K_G. Another reason of this apparent discrepancy between low- and high-dose effects can be due, despite careful blind randomization, to the greater leanness of the subjects in the low-dose group with therefore a tendency to be more insulin sensitive. The subjects in the high-dose group, well matched for BMI and basal glucose with the placebo group, were instead more obese and thus more insulin resistant with respect to those in the low-dose group. However, comparing S_I of the low-dose group before treatment versus that of high dose and placebo groups did not yield a significant difference ($P > .15$). From these considerations it follows that any improvement of insulin sensitivity in the high-dose group has a greater impact on glucose control when compared with leaner subjects. In addition, the fact that low-dose Caiapo exerted its beneficial effect even in patients with moderate insulin resistance supports the contention that Caiapo acts by improving insulin sensitivity in different degrees of insulin resistance. Another issue to be outlined is the fact that the improvement of insulin sensitivity was observed regardless of the method applied, although the insulin-sensitizing effect of low-dose Caiapo appears to be detected easier in the presence of elevated levels of insulin, as in the case of the FSIGT compared with the OGTT, in which the endogenous insulin levels are much lower.

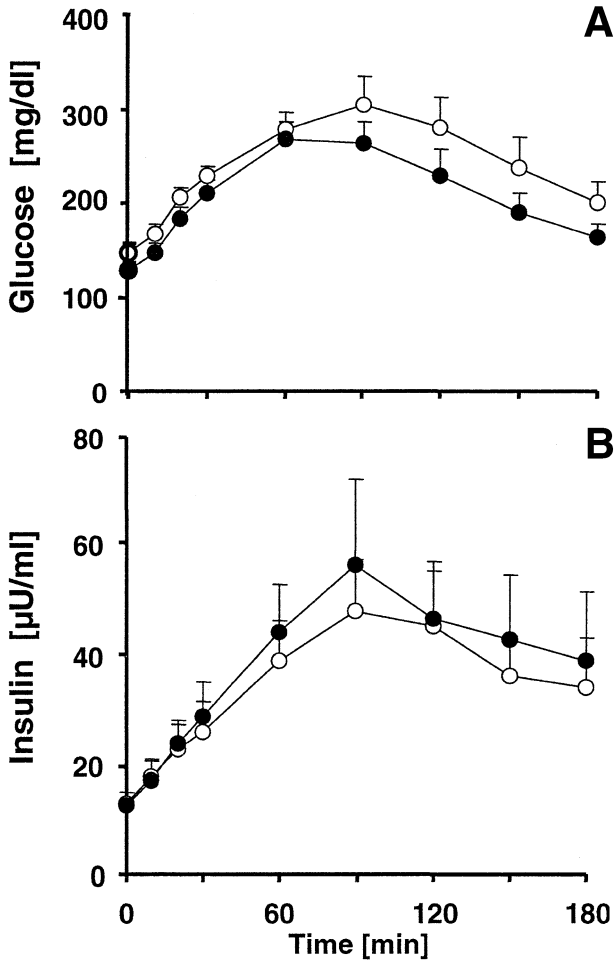

Fig 3. Plasma concentrations of (A) glucose and (B) insulin during OGTT before (○) and after (●) treatment with high-dose Caiapo (mean ± SEM, N = 6). Glucose concentration was lower in the Caiapo group (see AUC_G, Table 3), while insulin concentration levels were not different at any data point.

Table 3. Metabolic Parameters From OGTT Before (B) and After (A) Treatment With Placebo or Caiapo in the Single Groups

			Caiapo	
		Placebo	Low Dose	High Dose
2-h glucose (mg/dL)	B	278 ± 10	332 ± 17	282 ± 33
	A	278 ± 20	325 ± 24	232 ± 29*
AUC_G (min g/dL) interval 0-180	B	43.2 ± 1.2	51.8 ± 2.5	45.9 ± 4.1
	A	45.4 ± 2.4	50.8 ± 2.9	39.3 ± 3.3†
CP_b (ng/mL)	B	1.9 ± 0.2	2.2 ± 0.5	2.9 ± 0.4
	A	1.8 ± 0.1	2.2 ± 0.3	2.9 ± 0.5
AUC_{CP} (min ng/mL) interval 0-180	B	795 ± 96	737 ± 85	1170 ± 165
	A	646 ± 41	739 ± 54	1181 ± 147
BSR (μU/mL/min)	B	6.6 ± 0.7	7.5 ± 1.6	9.8 ± 1.4
	A	6.0 ± 0.3	7.5 ± 1.1	9.8 ± 1.6
TIS (mU/mL) interval 0-180	B	2.9 ± 0.4	2.6 ± 0.3	4.2 ± 0.6
	A	2.3 ± 0.2	2.6 ± 0.2	4.3 ± 0.5
HE (%)	B	78 ± 2	82 ± 1	78±3
	A	76 ± 2	81 ± 2	76 ± 3
AUC_I (min mU/mL) interval 0-180	B	4.3 ± 0.6	3.4 ± 0.5	6.8 ± 1.4
	A	3.8 ± 0.2	3.6 ± 0.5	7.7 ± 1.8
OGIS (mg/min/m^2)	B	292 ± 17	304 ± 21	308 ± 13
	A	291 ± 28	336 ± 33	334 ± 10‡
GD [10^{-6} (mg/m^2)(μU/mL)]	B	803 ± 164	547 ± 56	1,343 ± 355
	A	657 ± 116	652 ± 120	1,749 ± 462‖

NOTE. See Table 1 for parameter meaning; n = 6 per group.
Compared with pretreatment: *$P < .036$; †$P < .05$; ‡$P = .048$; §$P < .03$; ‖$P < .035$.

It is interesting to note that the parameters obtained by both methods (OGIS and S_I) were significantly correlated. The evaluation of insulin sensitivity indices in the same subjects by both the OGTT and FSIGT highlights another interesting result of the present study. During the last years, the possibility of extracting an index of insulin sensitivity from the simple and inexpensive OGTT has been the subject of various investigations. Among the several proposed methods,[16,18,19] we have utilized that of Mari et al,[16] which provides the index OGIS. When introduced, OGIS was validated against the gold standard glucose clamp, but this is the first study in which OGIS was compared in the same diabetic subjects with the other most widely used index: ie, the S_I value from Bergman's minimal model analysis of the intravenous glucose test.[12] The good correlation and significant regression between the 2 measurements demonstrate that both indices are able to detect in similar way changes in insulin sensitivity. The 2 indices are expressed in different units and their ranges (as difference between the maximum and minimum value over the mean) were 78 for OGIS and 343 for S_I. This shows the relative advantage of using the FSIGT when it is necessary to detect subtle differences of sensitivity, even in small groups, because it spans a much wider range. The reason for this is the fact that a highly dynamic test, both in terms of glucose and insulin patterns, more easily allows an accurate estimation of model parameters, yielding a more precise assessment of possible differences within the physiologic variables described by the calculated parameters. This may also explain why OGIS, at variance with S_I, is unable to detect differences in the low-dose group.

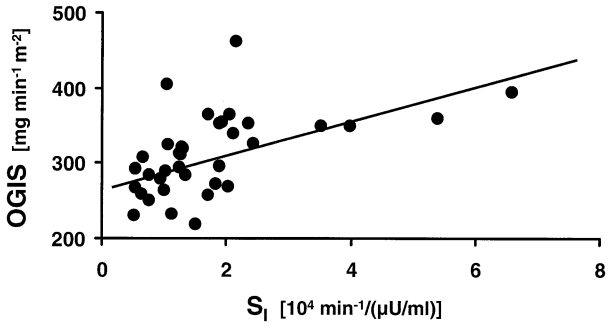

Fig 4. Relationship between insulin sensitivity from OGTT (OGIS) and FSIGT (S_I). The 2 indexes are positively correlated ($r = .52$, $P = .001$).

In terms of carbohydrate metabolism, the novelty of our results is the detailed description of the effects of a natural product on glucose tolerance. In fact, a large number of type 2 subjects use herbs or nutraceutical products for treating diabetes,[8] but in the absence of systematic investigations, their efficacy and safety is often not proven,[20] and the uncontrolled use of herbs or nutraceutical substances might harm rather than help the patients. For this reason, attention has been recently focused on controlled studies showing the beneficial effects of American Ginseng on postprandial glucose in type 2 diabetes.[21,22] Along this line, we undertook this study to evaluate the efficacy of Caiapo. This kind of potato (*Ipomoea batatas*) grows in mountainous regions of South America and has been used by Native Americans to alleviate symptoms most likely attributable to diabetes, such as thirst and weight loss. This potato has been cultivated in the Kagawa Prefecture in Japan and the extract of the skin of the root is used for the treatment of type 2 diabetes in Japan. An uncontrolled study in type 2 Japanese patients indicated a decrease of blood glucose levels

exceeding 10% of basal values in 77% of 145 subjects (personal communication, Fuji-Sangyo, March 15, 2002). In addition, other nonplacebo-controlled studies indicated that Caiapo was able to lower blood glucose in Japanese nondiabetic subjects (unpublished communication by Fuji-Sangyo). This evidence arose also from studies in rodent models, such as Zucker fatty rats.[23] Recently, an acidic glycoprotein that is proposed to be the active antidiabetic component has been isolated from Caiapo.[24] The efficacy of Caiapo regarding the improvement of diabetes control had not been established until now in Caucasian subjects, but the statistical significance of the results of our placebo-controlled, double-blind study, despite the low number of subjects in each group, supports the efficacy of Caiapo in patients with type 2 diabetes.

In conclusion, this study shows that the beneficial effects of Caiapo in patients with type 2 diabetes are exerted by decreasing insulin resistance without affecting body weight or insulin secretion and clearance. These results thus indicate that Caiapo could potentially play a role in the treatment of type 2 diabetes.

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