# Enzyme Inducers Improve Insulin Sensitivity in Non-insulin-dependent Diabetic Subjects

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**SUMMARY**

**The reduction in blood glucose in non-insulin-dependent diabetes mellitus (NIDDM) brought about by the use of phenobarbital (PB), a hepatic microsomal enzyme inducer, suggests an improvement in insulin sensitivity. The effect of PB on insulin-mediated glucose metabolism was hence investigated using the euglycemic clamp technique in 10 women with NIDDM aged 56–75 yr. The addition of PB to sulfonylurea therapy, concurrently for 6 wk, reduced fasting blood glucose (BG, from 12.8 ±1.6 to 10.2 ± 3.2 mmol/L, $P < 0.01$) and immunoreactive insulin (IRI) levels (from 32.4 ± 13.6 to 24.7 ± 9.8 mU/L, $P < 0.01$), whereas body weight remained unaltered. During the trial, there was a significant change in the glucose disposal rate (M, from 1.27 ± 0.60 to 2.82 ± 0.86 mg/kg/min, $P < 0.001$), the metabolic clearance rate of glucose (from 0.89 ± 0.41 to 2.24 ± 1.27 ml/kg/min, $P < 0.01$), the insulin sensitivity index (from 1.10 ± 0.44 to 2.86 ± 1.54 mg/kg/min: mU/L × 100, $P < 0.001$), and the plasma antipyrine clearance rate (from 28.3 ± 11.7 to 51.4 ± 20.2 ml/min, $P < 0.001$), an in vivo index of liver microsomal enzyme activity. The antipyrine clearance rate correlated with insulin-mediated glucose metabolism ($r^2 = 0.560$, $P < 0.01$). This correlation could be interpreted as indicating that, in NIDDM patients, peripheral glucose utilization and the liver microsomal enzyme system share common regulators. Our study suggests a new approach to the improvement of insulin sensitivity in NIDDM patients.** DIABETES 1985; 34:911–16.

Patients with non-insulin-dependent diabetes mellitus (NIDDM) have hyperglycemia, normal or high serum immunoreactive insulin (IRI), glucose intolerance, and reduced hepatic microsomal enzyme activity.[1-3] The decreased response to insulin results from a relative insulin deficiency and resistance.[4] The cornerstones of the treatment of NIDDM are education, diet, exercise, and oral antidiabetic drugs.[5] Some patients, however, develop resistance to this regimen, and new forms of therapy are required.[6] The addition of hepatic microsomal enzyme-inducing compounds, such as phenobarbital, to the therapy of NIDDM patients improves the glycemic control.[7] Phenobarbital (PB) enhances insulin-mediated glucose metabolism in healthy, nondiabetic subjects.[8] This suggests that, in NIDDM, the blood glucose (BG) decrease brought about by the inducers may also be associated with improved insulin sensitivity.

This study was undertaken to evaluate the effect of hepatic enzyme inducers on insulin sensitivity in NIDDM subjects resistant to previous management. Phenobarbital was selected as the inducer.[7-9] The glucose clamp technique was used to measure insulin sensitivity in vivo.[10] Conventional liver function tests, including the oral antipyrine test, were used to assess hepatic function.

## MATERIALS AND METHODS

**Subjects.** Ten women with NIDDM, as defined by the criteria of the National Diabetes Data Group,[11] were investigated after being referred to the hospital because of poor diabetes control. Their age was 64.7 ± 6.0 yr and the body mass index (BMI) ranged from 22.5 to 33.3 kg/m$^2$. The subjects had had diabetes for 9.7 ± 3.6 yr and their previous treatment regimens are outlined in Table 1. Three patients had ischemic heart disease (IHD) and four had arterial hypertension (HT). They had been treated with digoxin, beta-blockers, and furosemide, which was unchanged during the trial.

**Protocol.** The study protocol was approved by the Ethical Committee of Oulu University and by the subjects. The studies were carried out at the Clinical Research Unit (CRU). At the time of the first visit, the management of diabetes was once again discussed with a physician and a trained nurse. The diet was calculated on the basis of weight and height, and the mean energy intake was 5.5 mJ/day, which is equiv-

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TABLE 1
Clinical and biochemical data of 10 women with NIDDM

| Patient no. | Age (yr) | BMI (kg/m²) | Duration of diabetes (yr) | Therapy | Other diseases | Fasting BG (mmol/L) | Fasting IRI (mU/L) | M (mg/kg/min) | $MCR_i$ (ml/kg/min) | $Ap_{cl}$ (ml/min) | Index |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 56 | 33.3 | 7 | Gb, Gz | HT | 11.1 | 46.5 | 2.60 | 11.07 | 29.3 | 1.90 |
| 2 | 57 | 26.0 | 6 | Gz | No | 11.7 | 36.8 | 0.59 | 8.12 | 15.7 | 0.37 |
| 3 | 57 | 30.1 | 12 | Phen, Gb, I | HT | 13.8 | 61.4 | 1.73 | 14.57 | x | 1.33 |
| 4 | 59 | 22.6 | 9 | Phen, Gb, I | No | 15.6 | 23.2 | 1.02 | 19.19 | 59.1 | 1.36 |
| 5 | 66 | 27.2 | 8 | Gb, Gz | IHD | 12.6 | 18.7 | 0.94 | 10.83 | 26.0 | 0.85 |
| 6 | 66 | 28.3 | 12 | Phen, Gb, Gz | HT | 14.3 | 22.4 | 1.36 | 12.72 | 25.4 | 1.35 |
| 7 | 68 | 33.9 | 6 | Gb | HT | 10.6 | 35.9 | 0.87 | 14.29 | 25.1 | 0.82 |
| 8 | 69 | 30.1 | 7 | Gb, Gz | No | 11.5 | 43.8 | 1.56 | 10.29 | 21.6 | 1.11 |
| 9 | 73 | 22.5 | 17 | Phen, Gz, Met, I | IHD | 12.2 | 31.7 | 1.36 | 16.16 | 25.7 | 1.35 |
| 10 | 76 | 26.3 | 10 | Phen, Gb | IHD | 14.1 | 21.6 | 0.66 | 11.31 | 24.5 | 0.60 |
| Normal values in our laboratory (mean ± 2 SD) | | | | | | 3.5–5.6 | 5.0–25.0 | | | 23.8–51.2 | |

Abbreviations: BMI, body mass index; BG, blood glucose; IRI, immunoreactive insulin; M, glucose disposal rate; $MCR_i$, metabolic clearance rate of insulin; $Ap_{cl}$, antipyrine clearance rate; index, insulin sensitivity index, M/IRI (during clamp study) multiplied by 100; Gb, glibenclamide; Gz, glipizide; Phen, phenformin; Met, metformin; I, insulin; HT, arterial hypertension; IHD, ischemic heart disease; and x, allergic person, not tested.

alent to 60–80 kJ/kg body wt. Throughout the hospital stay, carbohydrates constituted 45%, fat 35%, and protein 20% of the total daily diet. The daily distribution of energy was: 15% at 8 a.m., 5% at 10 a.m., 25% at noon, 15% at 1:30 p.m., 25% at 4:30 p.m., and 15% at 8 p.m. The same schedule was recommended for use at home.

Blood samples for liver function tests were drawn after overnight fasting. Antipyrine, 20 mg/kg body wt dissolved in 100 ml of fruit juice, was given to each subject. Plasma specimens were obtained by venipuncture before and 1, 3, 6, 9, 12, 24, and 30 h after antipyrine ingestion. Samples for BG determination were taken four times daily—after an overnight fast, at noon, in the mid-afternoon, and in the evening. Plasma IRI was assayed from the blood drawn first in the morning. During the first visit, the sulfonylurea drugs were changed to glipizide or chlorpropamide. On the second admission 6 wk later, BG level was measured and the glucose clamp study performed. Phenobarbital, 100 mg at bedtime, was prescribed for the 6-wk period. The tests were repeated on the third admission. Eight weight- and sex-matched nondiabetic subjects served as controls for the glucose clamp studies.

**In vivo insulin sensitivity.** A modification of the glucose clamp technique was used to measure insulin sensitivity.[10] The subjects were studied in the postabsorptive state after an overnight fast. An intravenous (i.v.) catheter was inserted into an antecubital vein for glucose and insulin infusions. A second catheter was inserted into a dorsal hand vein of the opposite hand for blood sampling. A priming dose plus continuous infusion of crystalline porcine insulin (Actrapid, Novo, Denmark) was given. The priming dose was infused in a logarithmically decreasing manner for 10 min to reach a hyperinsulinemic level, and the continuous infusion of insulin was begun at 10 min and continued for 170 min to maintain hyperinsulinemia. The rate of continuous insulin infusion was 1.0 mU/kg/min. The insulin infusate was prepared in isotonic saline to which 2 ml of the subject's blood per 50 ml infusate was added to prevent adsorption of insulin onto the glass and plastic surfaces of the infusion set. The plasma glucose concentration was decreased to about 8 mmol/L at the beginning of the clamp study and maintained at this level by the determination of venous blood glucose every 10 min and by adjusting the infusion rate of a 20% glucose solution. The control group was clamped at a euglycemic glucose level of 5 mmol/L. During these steady-state conditions, all of the glucose infused is removed from the circulation and either metabolized by the peripheral tissues or taken up by the liver. The amount of glucose infused can thus be regarded as a measure of the whole-body sensitivity to insulin. The amount of glucose excreted into the urine during the clamp study was measured, and samples for IRI determination were taken every 20 min. The infusions were given using infusion pumps (IVAC 630, IVAC Corporation, San Diego, California).

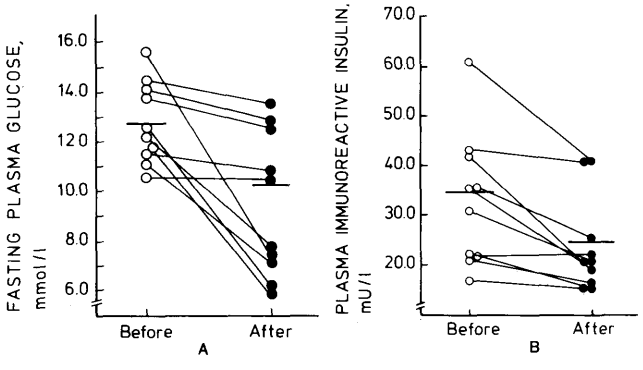


**FIGURE 1. Fasting plasma glucose levels (A) and fasting immunoreactive insulin levels (B) before and after therapy with an enzyme inducer, phenobarbital, 100 mg at bedtime in 10 NIDDM subjects.**

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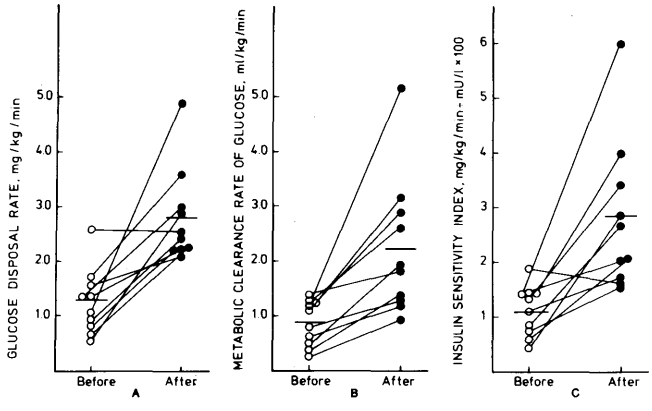


**FIGURE 2. Change in glucose disposal rate (A), in metabolic clearance rate of glucose (B), and in insulin sensitivity index (C) for individual NIDDM subjects during glucose clamp studies performed using an insulin infusion rate of 1 mU/kg/min before and after phenobarbital therapy.**

**Analytic methods.** Blood samples for glucose determinations were drawn from the venous catheter and measured immediately by means of a testing strip and a reflolux (BM-Test-BG, Boehringer-Mannheim GmbH, FRG), and checked with a hexokinase method (Glucoquant, Boehringer-Mannheim). The glucose infusion rate was primarily adjusted on the basis of reflolux determination and corrected according to the hexokinase method if necessary. The IRI concentration was determined using a commercial RIA kit (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, California). The plasma antipyrine content was measured using a gas-liquid chromatography method, phenacetin being the internal standard.[12,13] Other laboratory tests were performed using standard methods (Technicon SMAC system Autoanalyzer, Technicon Corp., Tarrytown, New York).

**Calculations.** The apparent clearance rate of antipyrine was calculated from the equation $CL = D/AUC_{total}$, where D is the oral dose of antipyrine and $AUC_{total}$ is the total area under the curve calculated by the trapezoidal rule. The amount of glucose metabolized (M) was calculated from the means of results from five 20-min periods from 80 to 180 min of the clamp study. The glucose excreted into urine was subtracted. The metabolic clearance rate of glucose ($MCR_g$) was calculated by dividing M by the mean steady-state glucose concentration during the same period.[14] The metabolic clearance rate of insulin ($MCR_i$) was calculated by dividing the continuous insulin infusion rate by the rise above the basal level.[15] The ratio M/IRI (during the clamp) expresses the insulin sensitivity index (multiplied by 100).[10] Statistical analysis was performed using the paired Student *t*-test and regression analysis. The data are expressed as mean ± SD.

## RESULTS

**Clinical characteristics.** Our patients were elderly women who had developed therapy resistance after 6–17 yr of diabetes management with education, exercise, diet, and drugs (Table 1). Four were obese (BMI > 30 kg/m$^2$); the others were of normal weight. The fasting BG level was elevated and tests for urinary glucose were slightly or moderately positive; none were, however, prone to ketosis. The fasting IRI level was elevated in six subjects and normal in the others. Liver function tests showed elevation of alkaline phosphatase in three patients and aspartate aminotransferase (ASAT) in one. Serum albumin, total bilirubin, thrombotest, and alanine aminotransferase (ALAT) were normal in all subjects. Antipyrine metabolism was reduced in five patients (Table 1).

Change in the sulfonylurea (SU) regimen and recommendations concerning diet and physical activity did not alter the fasting BG (12.5 ± 1.2 mmol/L on the first visit and 12.8 ± 1.6 mmol/L on the second) and fasting IRI levels (29.5 ± 15.1 mU/L and 34.2 ± 13.6 mU/L, respectively) between the first and second visits. The body weight remained unaltered (71.0 ± 12 kg and 71.4 ± 10 kg).

The addition of PB to the SU regimen reduced fasting BG (Figure 1, Table 2). Five patients were good responders while the others showed only a slight reduction. The fasting IRI level decreased in eight, remained unaltered in one, and increased in one (from 23.2 to 24.0 mU/L) (Figure 1), and the change in the mean values was significant (Table 2). The glucose disposal rate (M) rose in all subjects except one (Figure 2), whereas the metabolic clearance rate of glucose increased in every patient after PB therapy (Figure 2, Table 2), while that of insulin remained unaltered (Table 2). The insulin sensitivity index improved in all subjects (from 1.10 ± 0.44 to 2.86 ± 1.54 mg/kg/min: mU/L × 100, Figure 2), as did the antipyrine clearance rate (from 28.5 ± 11.7 ml/min to 51.4 ± 20.2 ml/min, $P < 0.001$, Figure 3). M and antipyrine clearance rate were related ($r^2 = 560$, $P < 0.01$, Figure 4). The other liver function tests remained unaltered.

During the insulin infusion, the steady-state serum IRI level remained unaltered (117.2 ± 24.9 mU/L the first time and 114.9 ± 32.6 mU/L the second time), as did the plasma glucose levels (8.7 ± 0.4 mmol/L and 8.1 ± 0.6 mmol/L). The coefficients of variation for plasma glucose concentrations during the clamp studies between the time period of 80–180

TABLE 2
Clinical and laboratory study results of 10 diabetic women before and after treatment with phenobarbital as compared with controls (mean ± SD)

| | | | Fasting | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age (yr) | Weight (kg) | BG (mmol/L) | IRI (mU/L) | M (mg/kg/min) | $MCR_g$ (ml/kg/min) | $MCR_i$ (ml/kg/min) | M/IRI × 100 ([mg/kg/min]/mU/L) | $Ap_{cl}$ (ml/min) |
| NIDDM | 64.7 ± 6.0 | 71.4 ± 10.0 | 12.8 ± 1.6 | 34.2 ± 13.6 | 1.27 ± 0.60 | 0.89 ± 0.41 | 12.85 ± 3.24 | 1.10 ± 0.44 | 28.3 ± 11.7 |
| NIDDM after phenobarbital therapy | 64.7 ± 6.0 | 71.3 ± 10.4 | 10.2 ± 3.2* | 24.7 ± 9.8* | 2.82 ± 0.86† | 2.24 ± 1.27* | 11.25 ± 3.60 | 2.86 ± 1.54† | 51.4 ± 20.2† |
| Controls | 61.2 ± 6.8 | 74.0 ± 12.0 | 4.8 ± 0.5 | 31.0 ± 12.5 | 6.40 ± 2.77 | 7.17 ± 2.82 | 8.12 ± 1.37 | 4.55 ± 1.97 | 48.9 ± 7.4 |

For abbreviations, see footnote to Table 1.
P-values for differences between means: *$P < 0.01$, †$P < 0.001$ (patients before versus after inducing drug).



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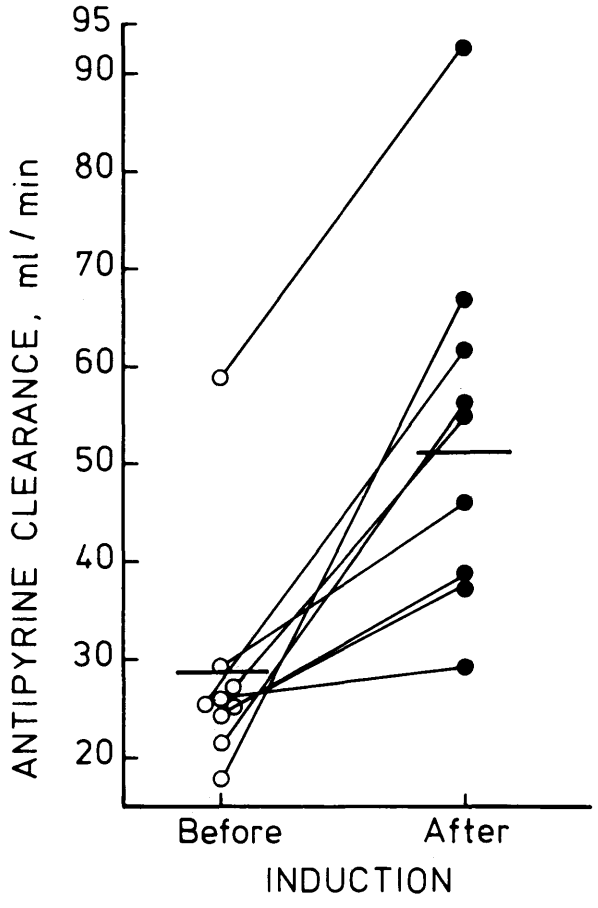


**FIGURE 3. Antipyrine clearance rates before and after phenobarbital treatment in nine NIDDM patients.**

min were 7.6 ± 1.2% and 6.4 ± 0.8%. The desired plasma glucose concentration was reached within 80 min in all the subjects.

## DISCUSSION

Insulin resistance is a prominent feature in NIDDM patients.[16–18] The detailed mechanisms for this are not yet known and various factors including circulating insulin inhibitors and defects at the receptor or postreceptor level are involved.[19,20] Insulin sensitivity can be improved by weight reduction, physical activity, insulin, and SU therapy and by an improved glycemic control.[21–25]

In an earlier study, the addition of hepatic microsomal enzyme-inducing drugs to a SU regimen reduced the BG level in NIDDM patients[7] displaying resistance to conventional diabetes management. This has been associated with the induction phenomenon and improved glucose turnover in hepatocytes.[7,26] Therapy with inducers improved insulin-mediated glucose metabolism in healthy subjects in whom the fasting IRI level decreased and the fasting BG remained unaltered.[8] The present results further demonstrate that therapy with PB improves the glucose disposal rate in patients with NIDDM and that this change parallels enhanced microsomal enzyme activity, as seen by improved antipyrine metabolism. In this study, venous blood was used to determine the plasma glucose level. This may cause a certain overestimation of the glucose disposal rate.[27] The studies were, however, performed in the same room with a stable temperature. The results obtained before and after PB are thus comparable. Although M-values improved markedly during induction (120%), the glucose disposal rate was still clearly lower than among the controls. This suggests that, in NIDDM patients, a relatively small improvement in insulin sensitivity is associated with improved glycemic control. The data seem to confirm the assumption that intracellular events play an important role in glucose metabolism in NIDDM.[17,28–30]

The detailed mechanisms by which enzyme inducers improve glucose metabolism are not yet known and several factors might be involved. For more than 20 yr it has been known that certain drugs (e.g., PB) activate the microsomal enzyme system located in the smooth endoplasmic reticulum (SER) of hepatocytes.[9,31] There would appear to be at least four distinct classes of inducers that induce distinct subsets of P-450 isoenzymes, suggesting that these isoenzymes are under separate regulatory control.[32,33] It has been assumed that an inducing compound, a fat-soluble and slowly metabolized agent, binds to the active site of liver enzymes, occupies it for a long time, and, by inhibiting enzyme activity, leads to accelerated synthesis of the enzyme protein.[9,31] PB increases liver weight, stimulates proliferation of SER, and induces NADPH-cytochrome P-450 reductase and one or more species of cytochrome P-450. Hepatic blood flow may also be increased, fat content reduced, and pericellular collagen fiber content decreased.[7,34,35] Subsequently, a later-given compound or an endogenic substance is eliminated at a faster rate than previously. This induction phenomenon is considered to be a pleiotypic adaptive response in the whole organism and not only limited to the liver.[9] In hepatocytes, intracellular glucose and drug metabolism are linked.[36–38] The inducers improve insulin-mediated glucose

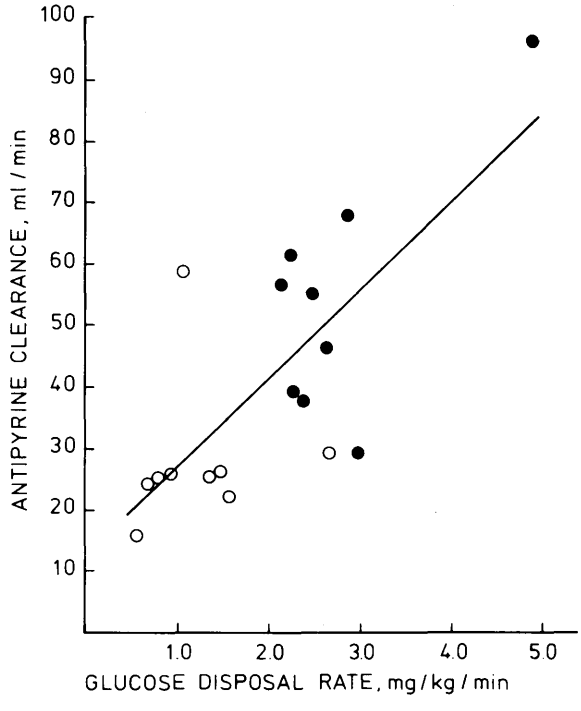


**FIGURE 4. Correlation between plasma antipyrine clearance rate and glucose disposal rate in nine women with NIDDM before (○) and after (●) phenobarbital therapy ($r^2 = 0.560$, $P < 0.01$).**

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metabolism, as tested with the euglycemic clamp technique, and the elimination rate of antipyrine from plasma. This indicates synchronization between intracellular glucose handling and hepatic microsomal enzyme function. A possible link may be found in the composition of cellular membranes, including the plasma cell membrane of the cells and the SER membrane and membrane-bound enzymes.[7] Since insulin receptors are located in the plasma cell membrane of the cells,[39] it is also possible that inducers influence the function of insulin receptors by changing cell membrane composition.[40]

The decrease in serum IRI level in healthy subjects[8] and in patients with NIDDM during induction therapy,[7] noted also here, probably reflects a decrease in the plasma glucose level caused by improved intracellular glucose handling. Subsequently, secretion of insulin may be reduced and the number of insulin receptors increased by a feedback mechanism.[41] Patients with NIDDM have a reduced number of insulin receptors on the cell surface,[39,42] and a reduced microsomal enzyme activity reflecting altered SER structure and function.[3] Therapy with inducers has been associated with increased hepatic phospholipid content,[40] a component of the plasma cell membrane and SER known to be associated with microsomal enzyme function. It is, therefore, possible that improved insulin sensitivity and antipyrine metabolism after PB therapy also reflect changes in the cellular membranes, as seen also in electronmicrographs.[7]

An explanation for the improved glycemic control might be a change in peripheral glucose handling, hepatic glucose production, or both. The amount of glucose metabolized during the clamp study is the sum of infused plus endogenously produced glucose. The endogenously (hepatic) produced glucose was not measured. We cannot, therefore, determine whether the principal change was hepatic or peripheral. However, data from other laboratories indicate a clear suppression of hepatic glucose production (85–98%) in NIDDM patients during hyperinsulinemia comparable with that in our study.[43–46] Thus, the hepatic glucose production during the clamp studies before and after PB would be of minor significance, and any change in the glucose infusion rate would reflect enhanced peripheral glucose uptake rather than increased hepatic suppression.

In conclusion, this study demonstrates that therapy with a hepatic enzyme-inducing drug, such as PB, increases insulin-mediated glucose metabolism in patients with NIDDM.

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