The effect of liver microsomal enzyme inducing and inhibiting drugs on insulin mediated glucose metabolism in man

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- 1 The effects of hepatic microsomal enzyme inducing (phenobarbitone and flumecinol), and inhibiting (cimetidine) drugs, and placebo treatment on insulin mediated glucose metabolism (M) were investigated in 29 healthy volunteers.
- 2 Phenobarbitone (50 mg for 10 days) increased M (30%), metabolic clearance rate of glucose (MCR_g), and antipyrine clearance rate (33%). Fasting immunoreactive insulin (IRI) decreased while fasting blood glucose (BG) remained unaltered.
- 3 Flumecinol, another inducer, tested in two doses (200 mg and 600 mg for 6 days), did not alter glucose or antipyrine metabolism. Fasting IRI reduced on treatment with 600 mg of flumecinol, but not with the smaller dose.
- 4 Cimetidine (600 mg for 6 days) decreased M (19.5%), MCR_g (26%), and antipyrine clearance rate (20%).
- 5 The placebo did not alter glucose or antipyrine metabolism.
- 6 The results indicate that the insulin mediated glucose disposal rate can be altered by drugs influencing hepatic microsomal enzyme activity.

Keywords insulin sensitivity liver enzyme activity

Introduction

Insulin sensitivity is altered in a number of physiological and pathological conditions. Various factors, such as age, obesity, diabetic conditions, and liver cirrhosis decrease the body sensitivity to insulin, whereas physical activity, weight reduction, and sulphonylurea therapy increase it (Fink *et al.*, 1983; Olefsky & Kolterman, 1981; Proietto *et al.*, 1980; DeFronzo & Kraemer, 1981; Beck-Nielsen *et al.*, 1979; Kolterman *et al.*, 1984). Changes in the number of insulin receptors on the plasma cell membrane of the target tissues are involved in some of the conditions (Olefsky, 1981), although it has been assumed that only 10% of receptor occupancy is sufficient to ensure an adequate insulin effect (Caro & Amatruda, 1980). This suggests that other factors such as post-receptor events may also be involved in the pathogenesis of insulin

resistance (Kolterman *et al.*, 1980). Intracellular glucose handling, regulated by insulin, can also be influenced by the mixed function oxidase system (Sotaniemi *et al.*, 1983; Stengård *et al.*, 1984).

This study was undertaken to further evaluate the relationship between hepatic glucose and drug metabolism in man. In addition to phenobarbitone (PB), a known enzyme inducer (Conney, 1967), the effect of cimetidine, a mixed function oxidase system inhibiting drug (Puurunen & Pelkonen, 1979; Puurunen *et al.*, 1980), and flumecinol (*m*-trifluoromethyl- α -ethylbenzhydrol), an inducer without other pharmacological properties (Gachalyi *et al.*, 1978), were studied and compared with those observed in placebo treated subjects. The euglycaemic clamp technique was used to measure the

in vivo insulin sensitivity before and after drug therapy (DeFronzo *et al.*, 1979). Liver drug metabolizing capacity was assessed using the oral antipyrine test.

Methods

Subjects

Twenty-nine healthy medical students were investigated. Physical characteristics are outlined in Table 1. They were randomly classified into the drug groups. None had received regular drug treatment. There was no family history of diabetes in any of the subjects. All were physically active. The nature, purpose, and possible risks of the study were explained before the study. Each subject served as his own control.

Protocol

The studies were carried out at the Clinical Research Unit. The euglycaemic clamp studies, and oral antipyrine tests were performed before and after medication. Group I was given 50 mg of phenobarbitone at bedtime for 10 days (Table 1). Group II received flumecinol 200 mg day⁻¹, group III flumecinol 600 mg day⁻¹ in one dose for 6 days, and group IV cimetidine 600 mg day⁻¹ divided into three doses for 6 days. The placebo-treated control group V were restudied after an interval of 10 days. The subjects had a normal blood picture, ESR, serum electrolytes, and liver function tests. Before the study the diet was discussed with the subjects. They were told to consume at least 250 g of carbohydrates per day and keep the diet constant 1 week before and during the study. The study protocol was approved of by the Ethics Committee of the University of Culu.

In vivo insulin sensitivity

The euglycaemic glucose clamp technique was used to measure the *in vivo* insulin sensitivity (DeFronzo *et al.*, 1979). The subjects were studied after a 12 h overnight fast in the post-absorptive state. An intravenous catheter was inserted into an antecubital vein for glucose and insulin infusions. A second catheter was inserted into a dorsal hand vein in the opposite hand for blood sampling. A priming dose plus a continuous infusion of semisynthetic crystalline human insulin (Actrapid Human, Novo, Denmark) was given. The priming dose was infused in a logarithmically decreasing manner for 10 min to reach a hyperinsulinaemic level. The continuous

infusion of insulin was begun at 10 min and continued for 120 min to maintain hyperinsulinaemia. The rate of continuous insulin infusion was 1.0 $\mu\text{u kg}^{-1} \text{ min}^{-1}$. The insulin infusate was prepared in an isotonic saline solution to which 2 ml of the subject's blood per 50 ml of infusate were added in order to prevent absorption of the insulin into the glass and plastic material of the infusion equipment. The plasma glucose level was maintained at the fasting level (about 5 mmol l^{-1}) by the determination of blood glucose concentration every 5 to 10 min from arterialized venous blood ($\text{PaO}_2 > 11.0 \text{ kPa}$), and by adjusting the infusion rate of a 20% glucose solution periodically. While in 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 infusions were administered through infusion pumps (IVAC 531, IVAC corporation, San Diego, USA).

During the steady state period of the clamp studies (20–120 min) the immunoreactive insulin (IRI) levels (determined every 20 min) were $87.1 \pm 10.2 \mu\text{u l}^{-1}$ and $85.7 \pm 9.7 \mu\text{u l}^{-1}$ before and after drug administration, respectively. The plasma glucose concentrations were $4.8 \pm 0.4 \text{ mmol l}^{-1}$ and $4.9 \pm 0.7 \text{ mmol l}^{-1}$ and the coefficients of variation less than 10%.

Hepatic microsomal enzyme activity

Enzyme activity *in vivo* was assessed using the oral antipyrine test. Antipyrine (20 mg kg^{-1}) dissolved in fruit juice was given to each subject after a 12 h fast. Blood samples for antipyrine determinations were drawn 0, 1, 3, 6, 12, and 24 h thereafter.

Analytical 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, West Germany), and checked with a glucose dehydrogenase method (Gluc-DH-method, E. Merck, Darmstadt, West Germany). The IRI concentration was determined using a RIA kit (Coat-A-Count, Diagnostic Products Corporation, LA, USA). The plasma antipyrine content was measured using a gas-liquid chromatography method, phenacetin being used as the internal standard (Prescott *et al.*, 1973), as used earlier (Sotaniemi *et al.*, 1977). Other laboratory tests were done using standard

Table 1 Clinical and biochemical data of the study groups (mean $\pm$ s.d.) before and after inducing or inhibiting drugs.

	Sex F/M	Age (years)	BMI kg m ⁻²	Fasting			M (mg kg ⁻¹ min ⁻¹)	MCR _g (ml kg ⁻¹ min ⁻¹)	MCR _i ml kg ⁻¹ min ⁻¹	CL _{ap} (ml min ⁻¹)
				BG (mmol l ⁻¹)	IRI (mU l ⁻¹)	IRI (mU l ⁻¹)				
Group I (n = 6)										
(PB 50 mg)										
	4/2	22.3	23.8	4.4	19.9		6.57	7.67	12.8	40.5
Before		1.4	4.2	0.5	8.7		1.54	2.20	4.1	8.2
(s.d.)			23.6	4.0	12.8*		8.48*	9.62**	10.7	54.0**
After			4.2	0.7	5.0		1.74	1.92	2.7	11.4
(s.d.)										
Group II (n = 6)										
(flumecinol 200 mg)										
Before	4/2	27.3	22.3	4.0	8.1		9.98	11.52	11.8	44.9
(s.d.)		7.6	2.3	0.4	2.5		2.74	3.41	1.8	7.1
After			22.2	4.1	8.8		11.42	12.75	12.2	43.4
(s.d.)			2.3	0.3	2.4		3.41	4.56	2.9	6.9
Group III (n = 6)										
(flumecinol 600 mg)										
Before	1/5	25.0	24.5	4.1	14.2		7.40	8.46	14.2	49.2
(s.d.)		2.4	3.9	0.2	3.9		1.93	1.92	3.2	10.0
After			24.4	4.2	11.3*		8.26	8.90	15.0	46.5
(s.d.)			4.0	0.6	2.9		2.31	2.87	2.8	12.6
Group IV (n = 8)										
(cimetidine 600 mg)										
Before	3/4	22.5	21.9	4.3	14.8		8.36	10.22	16.7	44.3
(s.d.)		1.8	3.0	0.4	4.8		1.03	1.13	4.2	11.1
After			21.7	4.2	16.5		6.73*	7.48*	15.1	35.3*
(s.d.)			2.2	0.6	3.2		1.51	1.94	4.5	9.1
Group V (n = 4)										
(placebo)										
Before	1/3	25.5	22.2	4.0	13.0		9.73	11.08	12.3	31.7
(s.d.)		5.7	0.9	0.2	5.9		1.19	1.34	3.0	8.4
After			21.9	4.1	7.8		9.59	10.25	11.6	35.2
(s.d.)			0.9	0.4	1.0		0.87	1.04	2.8	12.3

BMI = body mass index, BG = blood glucose, IRI = immunoreactive insulin, M = glucose disposal rate, MCR_g = metabolic clearance rate of glucose, MCR_i = metabolic clearance rate of insulin, CL_{ap} = antipyrine clearance rate. P values for differences between means: * < 0.05 , ** < 0.01 (subjects before/after inducing or inhibiting drug).

methods (Technicon SMAC system Auto-analyzer, Terrytown, USA).

Calculations

The apparent clearance rate of antipyrine was calculated from the equation $CL = D/AUC_{total}$, where D = oral dose of antipyrine and AUC_{total} = 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 20 to 120 min of the clamp study. The metabolic clearance rate of glucose (MCR_g) was calculated by dividing M by the mean steady state glucose concentration during the same period (Riggs, 1963). The metabolic clearance rate of insulin (MCR_i) was calculated by dividing the continuous insulin infusion rate by the rise above the basal level (Sherwin *et al.*, 1974). Statistical analysis was performed using the *t*-test for paired data. The data are expressed as mean $\pm$ s.d.

Results

Clinical characteristics

The subjects were healthy medical students. Age ranged from 21 to 40 years (mean $\pm$ s.d.

24.4 ± 4.5 years). All were within 15% of normal body weight apart from one subject (in group III, BMI 31.2 kg m^{-2}). Fasting blood glucose (BG), fasting IRI level, and the antipyrine clearance rate were normal in all the subjects (Table 1). Even though the groups were classified randomly, there was a large variation in the basal glucose disposal rate individually (three-fold) and between the groups (Figure 1).

Effect of inducing drugs

Phenobarbitone 50 mg increased the glucose disposal rate (M) significantly, as it did also the metabolic clearance rate of glucose (MCR_g), and antipyrine elimination from plasma (Table 1, Figures 1 and 2). The fasting IRI level decreased, whereas the metabolic clearance rate of insulin (MCR_i) was unchanged. The fasting BG remained unaltered. Flumecinol, another inducer, did not significantly alter values of M , MCR_g , MCR_i , antipyrine clearance rate or fasting BG. In the group IV with 600 mg of flumecinol fasting IRI decreased (Table 1).

Effect of inhibiting drugs

Cimetidine (group II, 600 mg day^{-1} for 6 days) reduced significantly M , MCR_g , and

Figure 1 Individual changes in the glucose disposal rate before (B) and after (A) the treatment with liver mixed function oxidase system inducing or inhibiting drugs with an insulin infusion rate of $1.0 \text{ mu kg}^{-1} \text{ min}^{-1}$. Group I phenobarbitone 50 mg, group II flumecinol 200 mg, group III flumecinol 600 mg, group IV cimetidine 600 mg, and group V placebo.

Figure 2 Individual changes in the antipyrine clearance rate before (B) and after (A) the treatment with liver mixed function oxidase system inducing or inhibiting drugs. Group I phenobarbitone 50 mg, group II flumecinol 200 mg, group III flumecinol 600 mg, group IV cimetidine 600 mg, and group V placebo.

antipyrine elimination. Fasting BG, IRI, and MCR_i remained unaltered (Table 1).

In placebo treated subjects (group V) there were no significant changes in M , MCR_g , MCR_i , antipyrine clearance rate, or fasting BG and IRI levels (Table 1).

Side effects

One subject complained of mouth dryness with 600 mg of flumecinol, and three had tiredness in the morning in the PB group.

Discussion

The liver is an important regulator of carbohydrate metabolism and the plasma glucose level (DeFronzo & Ferrannini, 1982). Insulin binding to the specific receptors on the plasma cell membrane of hepatocytes initiates the events which mediate the hormone action inside the cell (Czech, 1981). After entering the hepatocyte, glucose is phosphorylated to glucose-6-phosphate and then oxidized to carbon dioxide and water or stored as glycogen in the hepatocytes or fat in adipose tissue. In liver cells glucose and drug metabolism pathways are linked (Scholz *et al.*, 1973; Thurman *et al.*, 1981; Stengård *et al.*, 1984). Glucose-6-phosphatase, a multicom-

ponent enzyme system, and glycogen synthetase are microsomal, glucose metabolizing enzymes (Nordlie, 1979). Thus drugs having an effect on the mixed function oxidase system, may unspecifically influence the other enzymes located in the endoplasmic reticulum of the hepatocytes, as suggested by previous studies (Thurman & Scholz, 1969; Sotaniemi *et al.*, 1983, 1984; Lahtela *et al.*, 1985).

In this study the effect of inducing and inhibiting drugs was evaluated by measuring insulin sensitivity using the euglycaemic clamp technique (DeFronzo *et al.*, 1979). This method allows measurement of glucose disposal independent of the organism's own insulin secretion and glucose production. It is, therefore, considered as the best method for the determination of insulin sensitivity *in vivo* when compared to other methods such as oral or intravenous glucose tolerance tests, the intravenous insulin tolerance test or the insulin suppression test (Reaven, 1983). After a course of phenobarbitone (50 mg) the mixed function oxidase system was activated (antipyrine clearance increased by 33%), and insulin mediated glucose metabolism enhanced (M increased by 30%). This is consistent with the earlier results in which phenobarbitone (100 mg) caused equal responses (Lahtela *et al.*, 1984a, b) (Figure 3). The effect of flumecinol on the mixed function oxidase system was slight. The antipyrine metabolism remained unchanged. In

Figure 3 Relative changes in glucose disposal rate after the treatment of hepatic mixed function oxidase system inducing or inhibiting drugs (PB = phenobarbitone, Flu = flumecinol, Cim = cimetidine; data for group PB 100 mg, see ref. Lahtela *et al.*, 1984b).

subjects receiving 600 mg of flumecinol the fasting IRI decreased but the glucose disposal rate showed a tendency to increase in both groups.

The detailed mechanism by which mixed function oxidase inducing drugs improve glucose metabolism are unknown and several factors may be involved. Certain drugs, e.g. phenobarbitone activate the mixed function oxidase system located in the smooth endoplasmic reticulum (SER) of hepatocytes (Conney, 1967). They increase the liver weight, induce SER proliferation, stimulate NADPHcytochrome P-450 reductase, enhance one or more species of cytochrome P-450, and increase liver blood flow (Remmer, 1972; Remmer & Merker, 1963; Conney, 1967; Pirttiäho *et al.*, 1982). A subsequently given drug, which has the same metabolic route, is therefore 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 in the liver (Conney, 1967). Drugs which activate the mixed function oxidase system seem to have a parallel effect on intracellular glucose handling. Improvement of glycaemic control in patients with NIDDM having reduced mixed function oxidase activity may occur (Sotaniemi *et al.*, 1983). A possible link may be found in the composition of cellular membranes including plasma cell membrane, SER membrane and membrane bound enzymes (Sotaniemi *et al.*, 1984; Savolainen *et al.*, 1984). Since insulin re-

ceptors are located in the plasma cell membrane of the cells (Arner *et al.*, 1983) it is also possible that inducers, by influencing cell membrane composition, have an effect on insulin receptors or their function.

Various drugs inhibit the hepatic drug metabolizing enzyme system and metabolism and the pharmacodynamic effect of a subsequently given compound is altered. Cimetidine, a histamine H₂-receptor antagonist, has since 1979 been used as a model for microsomal enzyme activity inhibiting drugs (Puurunen & Pelkonen, 1979). The drug also alters the balance of endogenous compounds in the body e.g. potentiates the hypoprothrombinaemic effect of warfarin (Serlin *et al.*, 1979), and may reduce hepatic blood flow (Feely *et al.*, 1981), and as shown here, seems to be able to inhibit glucose metabolism. The insulin mediated glucose metabolism was reduced, and this change parallels the decreased antipyrine metabolism. This indicates that inhibition of the liver mixed function oxidase system is reflected in the glucose metabolism, thus confirming our previous findings (Lahtela *et al.*, 1984a,b, 1985) that there is a close synchronization between liver microsomal enzyme activity and peripheral glucose utilization. The change may also partly be due to alterations in liver blood flow associated with inducers (increase) and inhibitors (decrease).

In conclusion, the mixed function oxidase system inducing and inhibiting drugs have an

effect on insulin mediated glucose metabolism. This suggests a new approach to the modification of insulin resistance by inducing drugs, and also

emphasizes that inhibiting drugs must be taken into account when evaluating reasons for impaired glucose metabolism in man.

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(Received 21 January 1985,
accepted 28 August 1985)