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Effect of metformin on insulin receptor binding and glycaemic control in type II diabetes

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Abstract

To investigate the effect of metformin on insulin receptor binding and diabetic control, eight obese type II diabetic patients were studied before treatment, after one and four weeks of taking metformin (500 mg thrice daily), and four weeks after withdrawal of the drug. After one and four weeks of treatment the number of erythrocyte insulin receptors had increased by 116% and 184% respectively. This was due almost entirely to an increase in the number of low affinity binding sites. The number of receptors was still raised four weeks after metformin had been withdrawn. Diabetic control as assessed by urinary glucose, glycosylated haemoglobin (HbA_{1c}), and glucose tolerance values was significantly improved during metformin treatment, while plasma insulin concentrations were not altered.

These results indicate that metformin produces a rapid and protracted increase in low affinity insulin receptors in type II diabetes, associated with greater insulin sensitivity and improved diabetic control.

Introduction

Metformin has a place in the treatment of type II diabetic patients with normal hepatic and renal function. The drug may be appropriate in obese patients who show an inadequate

response to diet and in non-obese patients in whom a combination of diet and sulphonylurea has failed to produce glycaemic control.

Metformin reduces hyperglycaemia by increasing peripheral glucose uptake and reducing hepatic gluconeogenesis. The effect of the drug is achieved without an increase in plasma insulin concentrations, suggesting that it potentiates the action of insulin.¹ The first step in the cellular mechanism of insulin action is the binding of insulin to receptors in the plasma membrane. Metformin reportedly increases insulin binding to receptors in erythrocytes of normal subjects² and to receptors in cultured lymphocytes and cultured breast cancer cells.³ We report the effect of metformin on erythrocyte insulin receptor binding in type II diabetes in relation to diabetic control.

Patients and methods

We studied eight obese patients with type II diabetes (mean 137.5 ± SEM 10.2% of ideal body weight). Five of the patients were postmenopausal women and three were men, and their mean age was 61.0 ± 4.6 years. The mean time since diagnosis of their disease was 4.0 ± 0.8 years. Each patient was asked to follow a fully structured energy controlled diet from four weeks before the study until its completion. The diet was designed to maintain a constant body weight throughout. No patient had proteinuria or any biochemical evidence of impaired renal or hepatic function and none received any medication other than metformin. Each patient served as his or her own control. Tests were performed immediately before treatment, after one and four weeks of treatment with metformin (Glucophage, 500 mg three times a day), and four weeks after the metformin had been withdrawn.

Patients presented at 0900 after a 12 hour fast. A 24 hour urine collection from the previous day was analysed for the glucose concentration.⁴ Venous blood was collected for measurement of the percentage of glycosylated haemoglobin (HbA_{1c})⁵ and plasma concentrations of glucose,⁴ insulin,⁶ and metformin.⁷ A 50 g oral glucose tolerance test was performed and blood samples for measurement of plasma glucose and insulin concentration taken at 0, 30, 60, 90, and 120 minutes.

Erythrocyte insulin receptor binding was determined by the method of Gambhir *et al.*⁸ Data were analysed after Scatchard⁹ using a model which assumes two classes of receptors with different but fixed affinities, one exhibiting high affinity and the other low affinity.¹⁰ The apparent receptor affinity was taken as the concentration of native insulin required to reduce by 50% the specific cell bound fraction of ¹²⁵I-insulin.¹¹ The different interpretations of insulin receptor binding data have been reviewed elsewhere.¹²

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TABLE I—Diabetic control before, during, and after treatment with metformin (3 × 500 mg daily for four weeks). Values are means ± SEM. (Eight subjects)

Treatment	% Ideal body weight	Plasma metformin (μg/ml)	Urinary glucose (mmol/24 h)	HbA _{1c} (%)	Plasma glucose (mmol/l)		Plasma insulin (mU/l)	
					0 min	Σ†	0 min	Σ†
Pretreatment control	137.5 ± 10.2	ND	224.1 ± 71.9	14.0 ± 1.1	11.5 ± 1.0	78.2 ± 5.3	13.6 ± 2.4	125.3 ± 29.3
Metformin one week	137.6 ± 10.2	1.45 ± 0.41	136.1 ± 49.5	12.4 ± 1.4*	9.6 ± 0.8***	65.5 ± 4.3***	11.3 ± 2.2	128.6 ± 25.3
Metformin four weeks	138.5 ± 10.8	0.94 ± 0.34	77.7 ± 35.6*	12.7 ± 1.0	9.1 ± 0.8**	62.3 ± 4.5***	13.4 ± 1.5	115.3 ± 15.2
Metformin withdrawn four weeks	137.1 ± 10.3	ND	235.6 ± 95.3	13.8 ± 0.7	10.8 ± 1.0	76.3 ± 6.8	14.4 ± 1.8	121.4 ± 20.8

ND = Not detectable.

*p < 0.05, **p < 0.01, ***p < 0.001 compared with pretreatment control (Student's paired t test).

†Σ = Sum of plasma glucose or insulin values at 0, 30, 60, 90, and 120 min during 50 g oral glucose tolerance tests.

Conversion: SI to traditional units—Urinary glucose: 1 mmol/24 h ≈ 0.18 g/24 h. Plasma glucose: 1 mmol/l ≈ 18 mg/100 ml.

TABLE II—Erythrocyte insulin receptor binding before, during, and after treatment with metformin (3 × 500 mg daily for four weeks). Values are means ± SEM. (Eight subjects)

Treatment	Total receptor number per cell	High affinity receptor number per cell	Low affinity receptor number per cell	Apparent affinity constant (nmol/l)
Pretreatment control	176.1 ± 30.0	36.6 ± 5.4	139.5 ± 28.7	1.08 ± 0.06
Metformin one week	381.7 ± 86.0*	38.6 ± 3.7	343.1 ± 70.5*	1.03 ± 0.07
Metformin four weeks	500.6 ± 77.9**	46.1 ± 5.4	454.5 ± 79.9**	1.20 ± 0.05
Metformin withdrawn four weeks	405.1 ± 61.1**	36.3 ± 5.0	368.7 ± 64.3**	1.18 ± 0.08

*p < 0.05, **p < 0.01 compared with pretreatment control (Student's paired t test).

Results

Table I shows that body weight was maintained throughout the study. Compliance with the metformin treatment was confirmed by the plasma metformin concentrations. Diabetic control was improved during the four weeks of metformin treatment: 24 hour urinary glucose, HbA_{1c}, and fasting plasma glucose concentrations were reduced and glucose tolerance improved. Plasma insulin concentrations were not altered by the metformin.

Metformin increased erythrocyte insulin receptor binding in all patients (table II). The total number of insulin receptor binding sites was increased by 116% after one week and 184% after four weeks of treatment. This was due almost entirely to an increase in the number of low affinity receptors. There was no alteration of the apparent receptor affinity constant. The effect of metformin on the number of insulin receptors was still evident four weeks after metformin was withdrawn.

Discussion

These results provide further evidence that in type II diabetes the hypoglycaemic effect of metformin is mediated at least partly by potentiation of insulin action,¹ similar to the "extrapancreatic" mode of action proposed for sulphonylureas.¹³ The study also shows that metformin, like sulphonylureas,^{11,14} increases the number of insulin receptor binding sites in type II diabetes. In the cell model studied—the erythrocyte—metformin increased specifically the number of low affinity insulin receptors. The mechanism responsible for this increase does not appear to require the biosynthesis of new receptor protein, since erythrocytes cannot perform de novo protein biosynthesis. An increase in the availability of existing receptors is therefore proposed. The rapid onset of the effect (within one week) suggests that the recruitment of new cells into the erythrocyte pool could not account for the effect.¹⁵ Since metformin increases insulin receptor binding in vitro a direct effect on the target tissue is likely.^{2,3}

Insulin resistance and impaired insulin receptor binding are characteristic of type II diabetes.¹⁶ Thus increased insulin receptor binding might contribute to the hypoglycaemic action of metformin. Additional mechanisms must be considered, however, because the number of erythrocyte insulin receptors was still raised four weeks after metformin had been withdrawn though glycaemia had returned to almost pretreatment values. Preliminary animal studies suggested that oral hypoglycaemic agents might influence postreceptor events of insulin action

independently of effects at the receptor level.¹⁷ Our study provides further evidence to support this view.

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