Effects of Metformin on Insulin Resistance after Injury in the Rat

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Summary. Hyperglycaemia and insulin resistance occur after injury. The effects of the antidiabetic biguanide metformin in injured rats have been studied in order to elucidate the cause of these effects. Metformin (120 mg/kg S. C.) produced a significant hypoglycaemic effect after a 20% dorsal scald but did not affect the blood glucose concentration in non-injured rats. The hypoglycaemic effect did not result from increased insulin secretion. It was associated with a reduction in liver glycogen and an increase in blood lactate concentrations, suggesting that the drug acted by promoting peripheral glucose utilization. This was confirmed by measuring the clearance rate coefficient of $[5-^3H]$glucose. This rate coefficient was significantly increased by metformin treatment (140 mg/kg S. C.) in scalded rats, although it was not affected in non-injured rats. Intravenous glucose tolerance in scalded rats was not improved, probably because of the increased lactate concentration. Metformin (120–160 mg/kg) also produced a hypoglycaemic effect in rats after a 4 hrs period of bilateral hind-limb ischaemia, suggesting that similar metabolic changes occur after these two types of injury.

Key words: Scald injury, ischaemic injury, biguanide, metformin, insulin resistance, glucose utilization, blood glucose, blood lactate, liver glycogen.

The acute metabolic response to injury in man and other animals includes a rise in the blood glucose concentration due both to mobilization of glycogen stores and to impairment of peripheral glucose utilization. Although the latter may result in part from suppression of insulin release [2, 47] impairment of peripheral sensitivity to insulin is also involved [10, 15, 30]. This insulin resistance is the major cause of the impairment of glucose utilization following a non-lethal 20% dorsal scald injury in the rat [15]. The injured rat is thus in a state of hyperglycaemia with insulin resistance, which suggests a similarity to experimental diabetes.

It was therefore of interest to determine whether hypoglycaemic drugs used in the treatment of diabetes might be effective in reducing injury-induced hyperglycaemia, since this might help in elucidating the cause of the insulin resistance produced by injury. The hypoglycaemic biguanide metformin was chosen since it promotes glucose uptake by rat muscle in conditions in which this is impaired [16]. In the present study some of the metabolic effects of metformin in injured rats have been investigated.

Materials and Methods

Rats

The rats used were male Porton-Wistar albinos, fed on M. R. C. diet 41B and kept at 20 °C ambient temperature with 12 hrs of light per day from 07.00 hr. All experiments were performed at 20 °C. Rats to be injured weighed 246 g mean (range 235–267 g) and others 236 g mean (range 205–264 g). There were no significant differences in weight between metformin-treated groups and their controls. For serial sampling a cannula was inserted under ether anaesthesia into a jugular vein [20] at least 4 days (median 7 days) before the experiment. Injury consisted either of a full-thickness dorsal scald to 20% of the body surface area, produced between 10.00 hr and 12.30 hr by partial immersion in water at 83 °C for 30 seconds, during a period (about 3–4 min) of ether anaesthesia [5], or of a 4 hrs period of bilateral hind-limb ischaemia induced by application of tourniquets [36] from about 10.00 hr. Injections of metformin solutions or saline (NaCl

0.9%), each 1 ml/kg, were given subcutaneously (S. C.) immediately after scalding or at the time of removal of the tourniquets. Non-injured rats for serial sampling experiments were given a short period of ether anaesthesia (about 2 min) while an initial blood sample was taken if required, metformin solution or saline (1 ml/kg S. C.) injected, and the rat placed in a restraining cage.

In single sampling experiments rats were decapitated and blood collected in heparinized beakers. For serial sampling rats were given heparin (375 IU I. V.) before the experiment. Samples were withdrawn through the jugular vein cannula and an equal volume of saline replaced. Intravenous injections were given through a cannula inserted into a lateral tail vein at the time of injury or control anaesthesia.

For intravenous glucose tolerance tests rats were injected with glucose [1 g/kg I. V. as 50% (w/v) solution] about 2–2.5 hrs after scalding.

The rate of irreversible disposal of glucose was estimated by the method of Heath and Corney [26]. About 1.5–2 hrs after scalding or control anaesthesia a tracer amount of [5-^{3}H]glucose (about 36 μCi in 0.2 ml I. V.) was injected. Four blood samples were taken from each rat close to the optimal sampling times [27] as judged from the first few experiments. For injured rats these times were 5, 30, 60 and 180 min (saline-treated) or 3, 10, 26 and 72 min (metformin-treated); for all non-injured rats they were 3, 15, 30 and 95 min. Calculations were based on the quantities of glucose label per ml of blood, instead of those in the total blood volume per 100 g body weight as in the original method. In injured rats the mean blood glucose concentrations during the period of experiment remained steady within experimental error (Table 1). The clearance rate coefficient, k [ml whole blood. min^{-1}. (100 g)$^{-1}$], was assumed to remain constant during the experiment and calculated using equation (4.7) of Heath and Barton [25] with M = 1. The rate of glucose utilization was calculated as the product of k and the

mean blood glucose concentration in each rat and is therefore a mean figure over the experimental period. Since the changes in blood glucose concentration during the experiment were so small, however, alternative methods of calculation do not affect the general conclusions reached. In non-injured rats the blood glucose followed the pattern described by Heath and Corney [26], rising and then falling to a minimum at the third sampling time, and 'end' rate coefficients and rates were calculated using their equations (4) and (5) with n = 1.

Reagents

Metformin hydrochloride was supplied by Rona Laboratories Ltd., Hitchin. Doses of metformin refer to the hydrochloride. Reagents for glucose and lactate assays were purchased in kit form from The Boehringer Corporation (London) Ltd. Reagents for insulin assay were as described previously [15] together with rabbit anti-guinea-pig globulin (RD 18) from Wellcome Reagents Ltd., Beckenham. D-[5-^{3}H]glucose (TRK 290; specific activity 1.0 Ci/mmol) was purchased from The Radiochemical Centre, Amersham. Resins used in determination of glucose specific radioactivity were as follows. Zerolit resins were purchased from B. D. H. Chemicals Ltd., Poole. Zerolit 325 cation exchange, 14–52 mesh, was treated with 2M HCl for 2 hours and washed with deionized water to pH 5–6. Zerolit MIP anion exchange, 14–52 mesh, was treated with 2M NaOH for 2 hours and washed to pH 7. These were then mixed (1:1 by volume). AG 2 – X8 anion exchange resin, 200–400 mesh, chloride form, was purchased from V. A. Howe and Co. Ltd., London, and used as supplied.

Analytical Methods

Whole blood glucose and lactate concentrations were measured with hexokinase [38] and lactate dehydrogenase [29] respectively. Plasma insulin concentrations were measured in duplicate 50 μl samples with a

Table 1. Blood glucose concentrations (mM) during estimation of irreversible disposal rate of glucose in rats

		Sample No.			
		1	2	3	4
Injured	Controls (10)	8.02 ± 0.37	8.78 ± 0.46	8.95 ± 0.52	7.90 ± 0.63
	Metformin-treated (10)	5.87 ± 0.55	5.89 ± 0.62	5.74 ± 0.63	5.26 ± 0.68
Non-injured	Controls (8)	6.33 ± 0.18	6.62 ± 0.17	5.98 ± 0.11	6.18 ± 0.21
	Metformin-treated (7)	5.81 ± 0.28	6.23 ± 0.22	5.48 ± 0.22	6.18 ± 0.21

Rats were injected with saline (controls) or metformin (140 mg/kg s. c.) immediately after production of a 20% dorsal scald under ether anaesthesia (injured) or during brief ether anaesthesia (non-injured). [5-^{3}H]Glucose was injected I. V. 1.5–2 hrs later and four samples taken from each rat at times given in the text. Results are means ± SEM; numbers of rats are given in parentheses. In injured rats no between-samples differences are significant (P > 0.1) within either group, but at each sampling time the blood glucose concentration is significantly lower (P < 0.01) in the metformin-treated group than in their controls. In non-injured rats, both treated and control, the blood glucose concentrations fell significantly between samples 2 and 3 (P < 0.05). The blood glucose concentration in the metformin-treated non-injured rats was not significantly lower than in their controls at any sampling time (P > 0.05).

double-antibody radioimmunoassay based on that of Morgan and Lazarow [34]. Liver glycogen was measured as glucose with the hexokinase method after ethanol precipitation and acid hydrolysis [21]. Haematocrit values were corrected for entrained plasma [24].

Glucose specific radioactivity was determined as follows [24, 28]. Blood samples (200 µl) were deproteinized [41] and 1.0 ml of supernatant deionized by passage through a column (110 × 4 mm) of the mixed Zerolit resins. After washing the column with 3 ml deionized water the eluate was weighed and 0.5 ml used for estimation of the blood glucose concentration. One drop of acetic acid was added to the remainder before evaporation to near dryness at 45 °C under a stream of N_2. The residue, in about 200 µl of water, was streaked on to Whatman 3 MM chromatography paper and developed at 24 °C for 16 – 21 h with water – formic acid – 2-methylpropan-2-ol – butan-2-one (15 : 15 : 40 : 30 by volume). After drying the outer edges were removed and sprayed with $AgNO_3$ in acetone followed by ethanolic NaOH to locate the glucose. The glucose band was cut out just within its leading edge to avoid an unidentified labelled contaminant. It was eluted with deionized water (about 2.5 ml) through a column (40 × 3 mm) of AG 2-X8 anion-exchange resin. One ml was taken for counting of radioactivity in 10 ml Insta-Gel (Packard Instrument Company, Inc., Downers Grove, Ill., U.S.A.) and duplicate 0.5 ml samples for determination of glucose concentration.

Statistical Methods

Differences between means have been compared using the t-test except when samples to be compared differed significantly in variance when non-parametric methods were used. All methods were as described by Snedecor and Cochran [40].
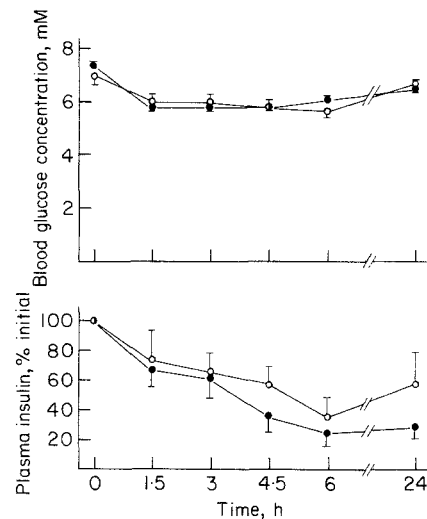
Results

Effects of Metformin on Blood Glucose and Plasma Insulin Concentrations
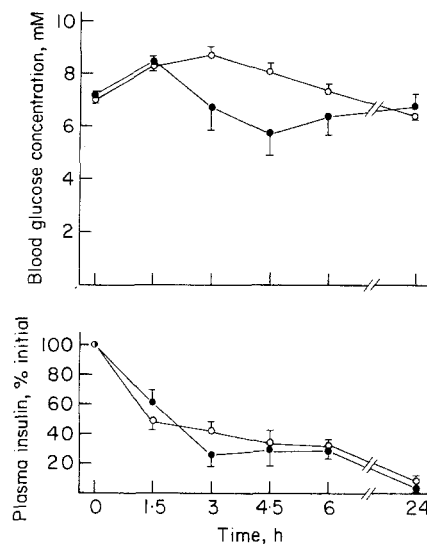
Blood glucose and plasma insulin concentrations were followed in serial samples from both non-injured and scalded rats given a single dose of metformin (Figs. 1 and 2). The control rats, both non-injured and scalded, were injected with saline. After 6 hrs the rats were given access to food and the 24 hrs sample was obtained by decapitation.

1. Non-Injured Rats. Metformin had no effect on either the blood glucose or the plasma insulin concentration (Fig. 1). The blood glucose concentration remained steady after the first sample in which it was

probably elevated by handling and by the brief anaesthesia [8]. The plasma insulin concentrations fell during the day and were still low after 24 hrs. They have been expressed as percentages of the initial concentration in each rat since the initial values were very vari-

Fig. 1. Effect of metformin on blood glucose and plasma insulin concentrations in non-injured rats. Saline (controls) or metformin (120 mg/kg) was injected s. c. immediately after withdrawing the first sample under ether anaesthesia. Points show means ± SEM; n = 5 (controls; open points), n = 6 (metformin-treated; solid points). Differences between control and metformin-treated rats were not significant at any time
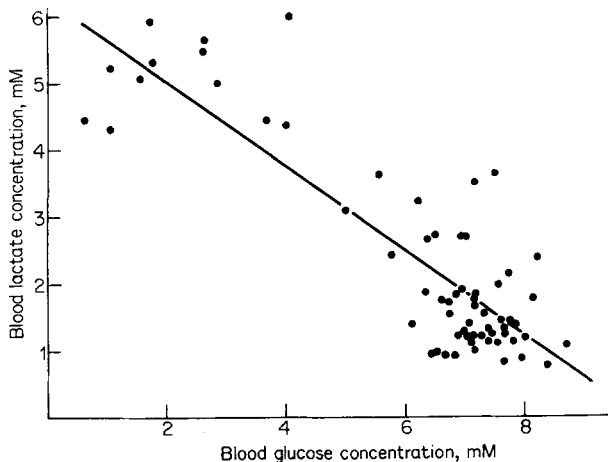

Fig. 2. Effect of metformin on blood glucose and plasma insulin concentrations in scalded rats. Saline (controls) or metformin (120 mg/kg) was injected s. c. immediately after producing a 20% dorsal scald injury under ether anaesthesia. The first sample was taken immediately before scalding. Points show means ± SEM; n = 7 (controls; open points), n = 6 (metformin-treated; solid points). The blood glucose concentration was significantly lower (P < 0.05) in the metformin-treated group than in the controls at 3 and 4.5 hrs. · Differences in plasma insulin concentrations were not significant at any time

able; mean values (μU/ml, ± SEM) were: controls, 10.5 ± 2.4; metformin-treated, 9.8 ± 2.0.

2. Scalded Rats (Fig. 2). In the control (i. e. saline-injected) scalded rats the blood glucose concentration rose to remain fairly steady from 1.5–4.5 hrs after injury. Metformin produced a significant hypoglycaemic effect, although the response to metformin was variable. The between-rats variance in blood glucose concentration was significantly greater in the metformin-treated rats than in the controls at 3, 4.5 and 6 hrs after scalding (P < 0.025 by F-test). Metformin did not affect the plasma insulin concentrations which again fell and were very low after 24 hrs. The mean initial plasma insulin concentrations (μU/ml, ± SEM) were: controls, 10.9 ± 1.0; metformin-treated, 13.6 ± 1.4.

Effects of Metformin in Various Doses in Scalded Rats

Blood glucose and lactate and liver glycogen concentrations were measured in scalded rats treated with metformin (0–200 mg/kg S. C.) and killed 3 hrs (± 1 min) later. Although the dose-response relationship was obscured by variability in the response to metformin, a fall in blood glucose concentration was associated with a rise in blood lactate concentration (Fig. 3) and a fall in liver glycogen (Fig. 4). In the four of these scalded rats given saline only the mean liver glycogen concentration was 2.90 ± 0.19 (mg/100 mg,
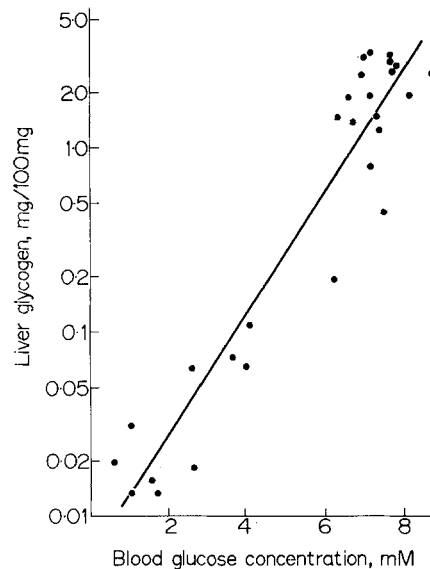
± SEM); this is at least an order of magnitude greater than that found after 24 hrs starvation in the rat (e. g. ref. 43; 0.2–0.01 mg/100 mg).

In addition a hypoglycaemic response was associated with a rise in great-vessel haematocrit (r = −0.52, P < 0.001, n = 63), although this was only a slight effect, the regression line for haematocrit (y; %) on blood glucose concentration (x; mM) being: y = −0.757x + 55.3.
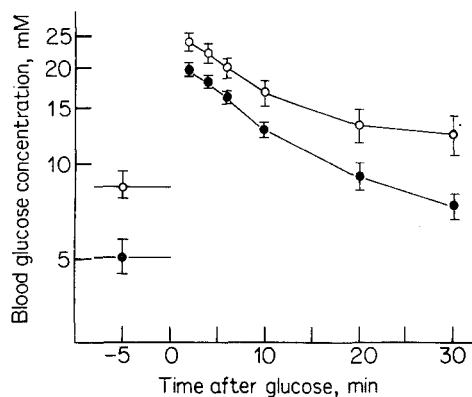
Effect of Metformin on Intravenous Glucose Tolerance in Scalded Rats

Intravenous glucose tolerance tests were performed on scalded rats injected with either saline (controls) or metformin. The blood glucose concentrations, followed by serial sampling, are shown in Fig. 5.
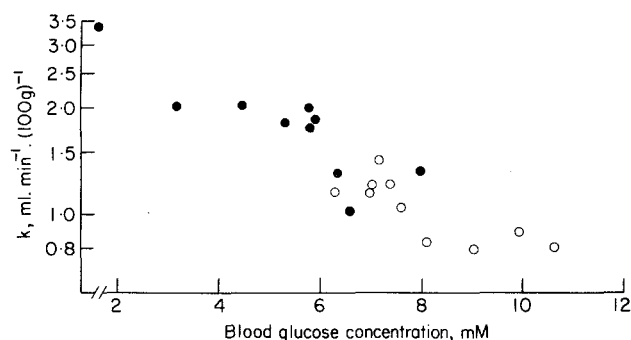
The blood glucose concentration was significantly lower (P ≤ 0.05) before and at all times after glucose injection in the metformin-treated rats. The fractional rate of fall of blood glucose concentration in each rat (K; %.min⁻¹) [13] was estimated over the linear part of the curve (2–10 min after injection). Despite the hypoglycaemic effect of metformin treatment K was not altered (K; means ± SEM, n = 7: controls, 4.6 ± 0.6; metformin-treated, 5.5 ± 0.9). Although this method of calculating K seems preferable [11, 39] to that based on the increment above the pre-injection level [4], K calculated on the latter basis was similarly

Fig. 3. Relationship between concentrations in blood of glucose and lactate in rats treated with metformin (0–200 mg/kg s. c.) immediately after producing a 20% dorsal scald. The rats were killed for these measurements 3 hrs later. Each point represents the result from a single rat. The line shows the regression of lactate on glucose. The correlation between blood glucose and lactate concentrations is highly significant (r = −0.86, P < 0.001)

Fig. 4. Relationship between concentrations of glucose in blood and glycogen in liver in rats treated with metformin (0–200 mg/kg s. c.) immediately after producing a 20% dorsal scald. The rats were killed for these measurements 3 hrs later. Each point represents the result from a single rat. Liver glycogen is plotted on a logarithmic scale. The line shows the regression of log(glycogen) on glucose. The correlation between blood glucose and log(liver glycogen) is highly significant (r = 0.95, P < 0.001)

Fig. 5. Effects of metformin (120 mg/kg s. c.) on intravenous glucose tolerance in scalded rats. Rats were injected with saline (controls; open points) or metformin (solid points) immediately after producing a 20% dorsal scald and glucose (1 g/kg I. V.) was injected 2 hrs later. Points show means ± SEM; n = 7 in each group. The blood glucose concentration was significantly lower (P ≤ 0.05) at all times in the metformin-treated group than in the controls, but metformin had no effect on the K-value
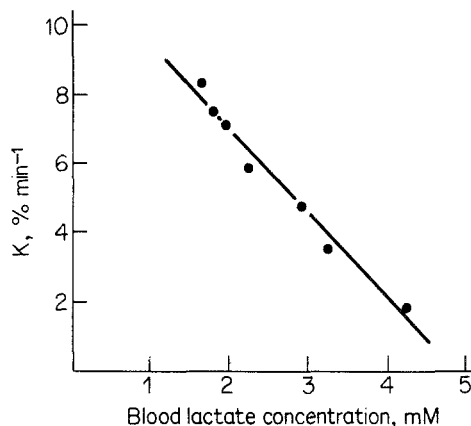

Fig. 6. Relationship between intravenous glucose tolerance (K) and blood lactate concentration in rats treated with metformin (120 mg/kg s. c.) immediately after producing a 20% dorsal scald. Each point represents the result from a single rat. The line shows the regression of K on blood lactate. The correlation between K and blood lactate concentration is highly significant (r = −0.988, P << 0.001)

Fig. 7. Relationship between clearance rate (k) of [5-^{3}H]glucose and blood glucose concentration in scalded rats injected with metformin (140 mg/kg s. c.) (solid points) or with saline (open points). Each point shows the result from a single rat. k is plotted on a logarithmic scale. The correlation between blood glucose and log k over all rats is highly significant (r = −0.91, P < 0.001, n = 20)

unaffected by metformin treatment (controls, 8.2 ± 1.0; metformin-treated, 8.7 ± 1.6 %.min^{-1}). In further sections K refers to that calculated on the basis of the total blood glucose concentration.

The blood lactate concentration, estimated 30 min after glucose injection, was not significantly different in the two groups (controls, 2.7 ± 0.5; metformin-treated, 2.6 ± 0.4 mM: means ± SEM, n = 7). There was a striking negative correlation between K and the blood lactate concentration in the metformin-treated group only (Fig. 6).

Effect of Metformin on Glucose Utilization

The rate coefficient and absolute rate of irreversible disposal of glucose were determined using [5-^{3}H]glucose in both non-injured and scalded rats injected

with either metformin (140 mg/kg) or saline (controls) (Tables 1 and 2).

In non-injured rats there was a slight tendency towards lower blood glucose concentrations with this dose of metformin, although this was not significant at any sampling time. Neither the clearance rate coefficient (k) nor the absolute disposal rate were significantly affected by metformin.

In metformin-treated injured rats, however, the mean blood glucose concentration over the period of study was significantly lower and k significantly higher than in their controls, although the mean absolute disposal rate was again not significantly different. k showed a significant negative correlation with the mean blood glucose concentration both in each treatment group and in this group as a whole (Fig. 7).

The plasma insulin concentrations, measured in the last sample from all injured rats except the first two in each treatment group, showed a positive correlation with the mean blood glucose concentration in the metformin-treated group (r = 0.80, P < 0.02) and in the whole group (r = 0.71, P < 0.002).

Effect of Metformin on Blood Glucose Concentration after Ischaemic Injury

After a 4 hrs period of bilateral hind-limb ischaemia rats were injected with saline or metformin and killed by decapitation 3 hrs (± 1 min) later, the time at which the peak blood glucose concentration is normally reached [42]. Metformin in doses greater than 80 mg/kg produced a significant dose-related reduction in blood glucose concentration with no change in great-vessel haematocrit (Table 3).

Table 2. Effects of metformin on irreversible disposal of glucose in rats

		n	Blood glucose concentration mM	Clearance rate coefficient ml. min^{-1}. (100 g)$^{-1}$	Absolute disposal rate μmol. min^{-1}. (100 g)$^{-1}$
Injured	Controls	10	8.4 ± 0.4	1.06 ± 0.07	8.7 ± 0.3
	Metformin-treated	10	5.7 ± 0.6[a]	1.85 ± 0.21[a]	9.6 ± 0.6
Non-injured	Controls	8	6.2 ± 0.2	1.27 ± 0.04	7.9 ± 0.5
	Metformin-treated	7	6.2 ± 0.2	1.33 ± 0.11	8.1 ± 0.6

[a] Significantly different from controls (P < 0.002)
Experimental details were as described in Table 1 and methods of calculation as in the text. For reasons given in the text 'mean' results over the period of experiment are shown for injured rats and 'end' results for non-injured. Results are means ± SEM.

Table 3. Effects of metformin on blood glucose concentration and on great-vessel haematocrit in rats injured by 4 hrs period of bilateral hind-limb ischaemia

Dose (mg/kg)	Glucose	Haematocrit	n
0	100 ± 5	100 ± 5	5
80	84 ± 12	102 ± 7	3
120	82 ± 4[a]	98 ± 5	3
160	17.3 ± 0.5[b]	103 ± 5	3

[a] Significantly different from controls (P < 0.05)
[b] Significantly different from controls (P << 0.001)
Metformin (or saline in controls) was injected s. c. at the end of the period of ischaemia and rats decapitated 3 hrs later. Results (mean ± SEM) are expressed as percentages of mean control value. Mean control values were: glucose, 10.3 mM; haematocrit 57.8.

Discussion

The metabolic changes following the scald and ischaemic injuries in the rat have been extensively studied and many features of the response are well established. The hyperglycaemia following these injuries results mainly from the rapid mobilization of liver and muscle glycogen [23, 42], probably with no great increase in the rate of hepatic gluconeogenesis [7, 42]. These changes occur under the influence of adrenaline [44] and probably glucagon [23, 26] and are to some extent abolished by prior medullectomy [42, 43]. The blood glucose concentration remains high for several hours after injury since the rate of peripheral glucose utilization fails to rise to match the increased concentration [26]. After the scald injury this impairment of glucose utilization is known to be due to insulin resistance rather than to suppression of insulin release [15].

There are thus several possible explanations for the hypoglycaemic effect of metformin in the injured rat, some of which may be readily discounted. Metformin did not act simply by reducing the severity of the injury since the raised haematocrit values typical of these non-haemorrhagic injuries were not lowered by hypoglycaemic doses of metformin. After scald injury

metformin in fact caused a slight increase in haematocrit, probably representing further loss of plasma volume secondary to the hypoglycaemia. Biguanides impair intestinal absorption of glucose [6, 32], but this action is unlikely to have been important in the substantially post-absorptive rats used in this study. The hypoglycaemic effect was not due to inhibition of the hepatic glycogenolysis since it was associated with a further reduction in liver glycogen concentration (Fig. 4) to levels well below those of untreated scalded rats. This reduction in liver glycogen was therefore probably a normal response to the metformin-induced hypoglycaemia.

The increase in blood lactate concentration (Fig. 3) suggested that metformin might act either by inhibition of hepatic gluconeogenesis from this substrate, or by stimulation of glucose uptake by muscle, with consequent lactate production. These possibilities were investigated by means of glucose tolerance tests and by direct measurement of the glucose disposal rate.

In diabetic patients intravenous glucose tolerance is improved by treatment with metformin [17, 31] and this has been taken as evidence for stimulation of peripheral glucose uptake, but no significant change in K-value was observed in the present study (Fig. 5). The intravenous glucose tolerance test is, however, unsatisfactory for investigating glucose utilization since, apart from introducing a gross metabolic disturbance, it depends on the balance between utilization and production of glucose. The lack of effect of metformin, despite a significant hypoglycaemic effect, may be related to the highly significant inverse correlation in the treated rats between blood lactate concentration and K-value (Fig. 6). Since the rate of hepatic gluconeogenesis from lactate in the rat is proportional to the plasma lactate concentration over this range [1] any elevation by metformin of the blood lactate concentration will increase the rate of hepatic glucose output, thus counteracting the stimulation of peripheral glucose uptake. This finding therefore suggests that hepatic gluconeogenesis from lactate was

not inhibited by metformin under these conditions. Although the biguanides can inhibit hepatic gluconeogenesis in various species [14, 45] the rat liver is not as sensitive to this effect as that of other species such as guinea-pig [3], and Polacek and Ouart have recently shown [35] that the hypoglycaemic effect of phenformin in the rat *in vivo* is independent of hepatic effects.

Glucose utilization was estimated directly from the irreversible disposal rate of [5-^{3}H]glucose. These studies were made at times such that the blood glucose concentrations in the injured rats were fairly steady in both control and metformin-treated groups (Table 1). The clearance rate coefficient, k, was significantly greater in the metformin-treated injured rats than in their controls (Fig. 7), although the absolute rate of glucose utilization was not significantly different. This suggests that metformin primarily increased k, thus lowering the blood glucose concentration to a level at which the utilization rate again balanced the glucose production rate. This implies that the rate of hepatic glucose production was unaltered by metformin. The stimulation of glucose utilization did not, however, result from increased insulin secretion. The plasma insulin concentration was not significantly altered by a hypoglycaemic dose of metformin (Fig. 2) and in the [5-^{3}H]glucose disposal studies there was a positive correlation between blood glucose and plasma insulin levels, suggesting that the latter were being controlled by the former rather than vice versa. The hypoglycaemic effect of the biguanides in man similarly does not involve increased insulin secretion [9, 22].

Metformin is thus able to overcome the insulin resistance which occurs after this scald injury at a dose which is without significant effect on the concentration or turnover of blood glucose in the normal rat. Although the cause of this insulin resistance is unknown it has been suggested [15] that it may be similar to the insensitivity to insulin of glucose uptake by muscle in experimental diabetes, and the present results would be consistent with this suggestion. The biguanides lower the blood glucose concentration in diabetes at doses which have no hypoglycaemic effect in normally-fed non-diabetic man [33] or rat [46], and metformin *in vitro* stimulates glucose uptake into muscle from alloxan-diabetic rats in concentrations which have no effect on normal muscle [16]. The stimulation by metformin of glucose uptake into muscle *in vitro* is probably an intracellular effect rather than an action on the cell membrane, since it is seen only when intracellular utilization of glucose, rather than its membrane transport, is the rate-limiting step in glucose uptake [16, 18]. If the action of metformin after injury is similar to its action in diabetes, this would suggest that the insulin resistance caused by

injury in the rat is the result of an intracellular impairment of glucose utilization in muscle, rather than of a direct impairment of membrane transport or its regulation by insulin, as has been suggested in man [19]. Insulin resistance of this nature in muscle should be demonstrable *in vitro* as is the case in experimental diabetes [16], and this has been observed after haemorrhagic shock in the rat [12] and rabbit [37]. The scald and ischaemic injuries in the rat produce similar effects on glucose utilization [26] and the finding that metformin also produces a hypoglycaemic effect after ischaemic injury adds support to the idea that these two types of injury result in a common basic metabolic disturbance.

The present study thus adds to our understanding of the pathophysiology of injury by suggesting a mechanism for the insulin resistance and impairment of glucose utilization which occur after injury. However, these effects probably represent a defence mechanism ensuring adequate energy supplies for insulin-independent tissues such as the central nervous system, and it is not suggested that overcoming them with metformin would necessarily be beneficial.

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