The Antihyperglycaemic Effect of Metformin
Therapeutic and Cellular Mechanisms

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Abstract

Metformin is regarded as an antihyperglycaemic agent because it lowers blood glucose concentrations in type 2 (non–insulin-dependent) diabetes without causing overt hypoglycaemia. Its clinical efficacy requires the presence of insulin and involves several therapeutic effects. Of these effects, some are mediated via increased insulin action, and some are not directly insulin dependent.

Metformin acts on the liver to suppress gluconeogenesis mainly by potentiating the effect of insulin, reducing hepatic extraction of certain substrates (e.g., lactate) and opposing the effects of glucagon. In addition, metformin can reduce the overall rate of glycogenolysis and decrease the activity of hepatic glucose-6-phosphatase. Insulin-stimulated glucose uptake into skeletal muscle is enhanced by metformin. This has been attributed in part to increased movement of insulin-sensitive glucose transporters into the cell membrane. Metformin also appears to increase the functional properties of insulin- and glucose-sensitive transporters. The increased cellular uptake of glucose is associated with increased glycogen synthase activity and glycogen storage. Other effects involved in the blood glucose-lowering effect of metformin include an insulin-independent suppression of fatty acid oxidation and a reduction in hypertriglyceridaemia. These effects reduce the energy supply for gluconeogenesis and serve to balance the glucose-fatty acid (Randle) cycle. Increased glucose turnover, particularly in the splanchnic bed, may also contribute to the blood glucose-lowering capability of metformin.

Metformin improves insulin sensitivity by increasing insulin-mediated insulin receptor tyrosine kinase activity, which activates post-receptor insulin signalling pathways. Some other effects of metformin may result from changes in membrane fluidity in hyperglycaemic states.

Metformin therefore improves hepatic and peripheral sensitivity to insulin, with both direct and indirect effects on liver and muscle. It also exerts effects that are independent of insulin but cannot substitute for this hormone. These effects collectively reduce insulin resistance and glucotoxicity in type 2 diabetes.

Since its introduction in 1957, metformin has become an established treatment for type 2 (non–insulin-dependent) diabetes mellitus.1,2 It is used as monotherapy and in combination with other types of oral antidiabetic agent or insulin, thereby offering a unique profile of therapeutic effects. The blood glucose-lowering effect of metformin is complemented by potentially beneficial effects on
blood lipid profiles and improvements in various micro- and macrovascular parameters. Metformin does not cause weight gain, and tends to reduce hyperinsulinaemia, which serves to counter insulin resistance and its clinical sequelae.

Typically, metformin reduces basal hyperglycaemia by 1 to 3 mmol/L and decreases haemoglobin A1c (HbA1c) by 1 to 2%. However, metformin alone does not precipitate overt hypoglycaemia; hence its designation as an anti-hyperglycaemic agent. Metformin appears to require the presence of insulin to lower blood glucose levels, although the drug does not stimulate insulin secretion. Metformin exerts a variety of insulin-dependent and insulin-independent actions, although the insulin-independent effects are not a substitute for insulin. Moreover, metformin has different actions in different tissues, which collectively account for the blood glucose-lowering effect.

This review considers the sites and mechanisms of action responsible for the antihyperglycaemic effect of metformin.

### 1. Antihyperglycaemic Effects

The main gluco-regulatory effects of metformin involve suppression of hepatic glucose output, increased peripheral glucose utilisation, reduced fatty acid utilisation and increased glucose turnover, particularly in the splanchnic bed (table I). In addition, metformin alters glucose handling by erythrocytes and reduces hypertriglyceridaemia. Thus, metformin can affect a variety of gluco-regulatory processes, both directly and indirectly via an improved metabolic environment.

The variety of effects exerted by metformin appears to be related, at least in part, to the markedly different concentrations of the drug in different tissues seen at different times after administration.

Metformin is rapidly absorbed and rapidly excreted unchanged in the urine. In clinical use an oral dose of 500 to 1000mg results in a maximum concentration of 1 to 3 mg/L (about 1 to 2 × 10⁻⁵ mol/L) in venous plasma after about 2 hours.

When 50 mg/kg metformin was given orally to normal and streptozotocin diabetic mice (equivalent to 3000mg in a 60kg person on a weight-for-weight basis), the maximum concentration of metformin was about 3 × 10⁻⁵ mol/L in peripheral venous plasma and 5 to 6 × 10⁻⁵ mol/L in the hepatic portal vein.

Extremely high concentrations of metformin accumulated in the walls of the jejunum and ileum (up to 3 × 10⁻³ mol/L) compared with the liver (up to 3 × 10⁻⁴ mol/L) or muscle and fat (up to approximately 5 × 10⁻⁵ mol/L).

#### 1.1 Hepatic Glucose Output

There is substantial evidence that metformin reduces hepatic gluconeogenesis. Studies in isolated perfused livers and hepatocytes from animals have shown that metformin acts directly on the liver to reduce gluconeogenesis from a range of substrates including lactate, pyruvate, alanine, glutamine and glycerol. In the absence of added insulin there is little effect until the metformin concentration is above that normally found within the hepatic portal vein. However, in the presence of insulin, therapeutic concentrations of metformin have been reported to suppress gluconeogenesis, thus showing a synergistic effect with insulin (fig. 1). This effect was increased in the presence of raised glucose concentrations and metformin also suppressed the gluconeogenic effect of glucagon. While low concentrations of metformin promote the anti-gluconeogenic action of insulin, higher concentrations can exert several non–insulin-dependent effects that contribute to a reduction in hepatic glucose production. These include decreased hepatic uptake of gluconeogenic precursors such as lactate and possibly amino acids. High concentrations of metformin might also reduce the mitochondrial NAD to NADH ratio causing a slight lowering of cellular ATP that is sufficient to enhance the flux through pyruvate kinase.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic glucose output</td>
<td>Decreased</td>
</tr>
<tr>
<td>Peripheral glucose utilisation</td>
<td>Increased</td>
</tr>
<tr>
<td>Fatty acid oxidation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Glucose turnover</td>
<td>Increased</td>
</tr>
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</table>