Diabetologia (2011) 54:219–222
DOI 10.1007/s00125-010-1986-3

COMMENTARY

New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser

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Received: 30 September 2010 / Accepted: 22 October 2010 / Published online: 30 November 2010

Abstract The two major deficits in type 2 diabetes, insulin resistance and impaired beta cell function, are often treated with metformin and incretin-based drugs, respectively. However, there may be unappreciated benefits of this combination of therapies. In this issue of *Diabetologia*, Maida et al. (doi:10.1007/s00125-010-1937-z) report that metformin acutely increases plasma levels of glucagon-like peptide 1 (GLP-1) in mice. Moreover, they show that metformin enhances the expression of the genes encoding the receptors for both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) in mouse islets and also increases the effects of GIP and GLP-1 on insulin secretion from beta cells. Interestingly, these incretin-sensitising effects of metformin appear to be mediated by a peroxisome proliferator-activated receptor α-dependent pathway, as opposed to the more commonly ascribed pathway of metformin action involving AMP-activated protein kinase. These provocative findings by Maida et al. extend our understanding of the mechanism of action of metformin and provide further insights into the benefits of combining metformin with incretin-based drugs to combat diabetes.

Keywords Dipeptidyl peptidase-4 · Glucagon-like peptide 1 · Incretin · Metformin · Type 2 diabetes

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Abbreviations

AMPK	AMP-activated protein kinase
DPP-4	Dipeptidyl peptidase-4
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
PPARα	Peroxisome proliferator-activated receptor α

For more than 50 years metformin has been used to control hyperglycaemia in patients with type 2 diabetes, and it is currently recommended as the first-line drug treatment along with lifestyle modification [1]. Furthermore, metformin can dramatically reduce the incidence of type 2 diabetes in individuals with impaired glucose tolerance who are at high risk of developing type 2 diabetes [2]. Metformin is thought to exert these powerful effects primarily by counteracting insulin resistance to curtail hepatic glucose output and increase insulin-stimulated glucose uptake in muscle and fat [3]. Given that the two major defects in type 2 diabetes are insulin resistance and impaired insulin secretion, metformin is recommended for use in combination with insulin secretogogues and even with intensive insulin therapy [1]. Metformin is now increasingly being used in combination with new incretin-based therapies: glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors [4–6], both of which enhance pancreatic beta cell function. Interestingly, there have been a few reports suggesting a direct interaction between metformin and the incretin axis [7–9]. In this regard, the article by Maida et al. published in this issue of *Diabetologia* [10] provides new insights into the biological actions of metformin that improve glucose homeostasis.

Maida et al. [10] reported that metformin acutely and selectively increased plasma levels of GLP-1 in mice, even in the absence of concomitant oral glucose administration,

while it did not increase plasma levels of the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), or, curiously, peptide YY, a gastrointestinal hormone co-localised with GLP-1 in L cells. Therefore, the action of metformin on the gut endocrine system may be L cell-specific and, more precisely, GLP-1-specific. However, in a preliminary study [11], metformin did not increase GLP-1 secretion from L cells in vitro. Therefore, there appear to be as yet unknown pathways by which metformin can acutely increase GLP-1 secretion. In this regard, it is noteworthy that metformin increases intestinal glucose utilisation [3], which perhaps could be coupled to GLP-1 production. Moreover, it has recently been reported that metformin inhibits the apical sodium-dependent bile acid transporter and thus may increase the concentration of bile acids in the intestine [12], which could stimulate GLP-1 secretion from L cells via the G-protein-coupled receptor TGR5 [13]. Alternatively, DPP-4 activity might be inhibited by metformin, resulting in an increase in GLP-1 levels in the plasma. Indeed, DPP-4 activity in the circulation has been reported to be reduced in rodents or humans treated with metformin [14, 15]. Yet, contrary to these findings, metformin does not directly inhibit DPP-4 activity in vitro [9, 14, 16]. Maida et al. [10] also found that metformin at doses exhibiting GLP-1-increasing effects exerted no effect on plasma DPP-4 activity in mice. Furthermore, metformin increased plasma GLP-1 levels in rats genetically lacking DPP-4 [9]. Therefore, decreased DPP-4 activity is unlikely to explain the elevated GLP-1 levels after metformin treatment. The ability of metformin to increase GLP-1 levels independently of effects on DPP-4 suggests there could be a direct benefit in terms of incretin action by combining metformin with DPP-4 inhibitors. Indeed, the combination of a DPP-4 inhibitor with metformin provides substantial and additive glycaemic improvement compared with metformin alone in patients with type 2 diabetes [17, 18].

Type 2 diabetes is characterised by a relentless decline in pancreatic beta cell function over time. The UK Prospective Diabetes Study (UKPDS) suggested that the rate of beta cell deterioration associated with metformin was similar to that associated with diet alone or sulfonylureas [19]. However, in A Diabetes Outcome Progression Trial (ADOPT), metformin exhibited a reduced risk of monotherapy failure compared with the sulfonylurea glibenclamide (known as glyburide in the USA and Canada) and slower rate of loss of beta cell function, although it was inferior to the thiazolidinedione rosiglitazone [20]. Metformin has also been shown to improve insulin secretion from rat islets chronically exposed to high levels of NEFA or glucose [21], suggesting a direct effect on pancreatic beta cells indepen-

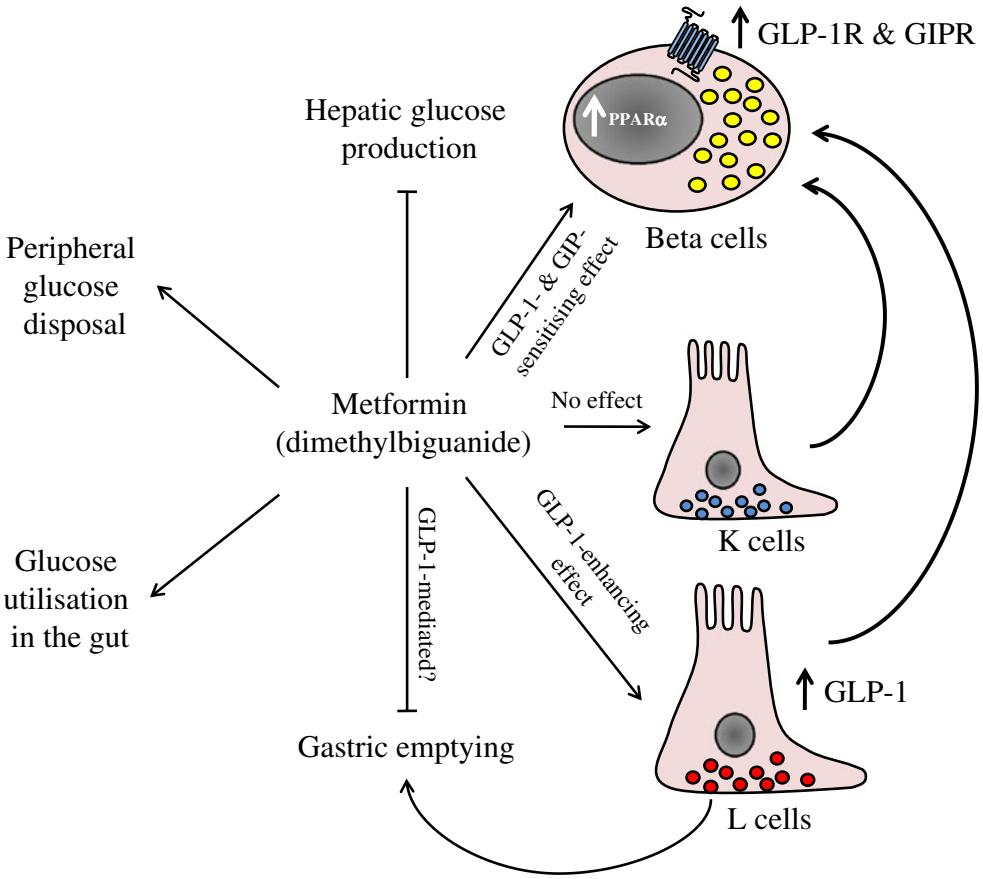

Fig. 1 The proposed mechanisms of metformin action on glucose homeostasis. In addition to the known actions of metformin—suppressing hepatic glucose output, increasing glucose uptake in muscle and fat, and increasing glucose utilisation in the gut [3]—metformin may enhance incretin signalling by increasing the plasma level of GLP-1 from L cells (red) but not GIP from K cells (blue), as well as by increasing the expression of GLP-1 and GIP receptors (GLP-1R and GIPR) in the insulin (yellow)-containing pancreatic beta cells via a PPARα-dependent mechanism

dent of its glucose-lowering action. What is the mechanism of these effects of metformin on pancreatic beta cells? Interestingly, Maida et al. [10] showed that metformin enhanced the expression of the genes encoding the receptors for both GIP and GLP-1 (*Gipr* and *Glp1r*, respectively) in mouse islets and also increased the effects of GIP and GLP-1 on insulin secretion from beta cells. While most of the actions of metformin appear to be mediated by cellular activation of AMP-activated protein kinase (AMPK), their findings indicate that the effects on incretin receptor expression in beta cells appear to be independent of AMPK, but, rather, are mediated by peroxisome proliferator-activated receptor α (PPARα), as metformin failed to induce expression of the gene encoding the incretin receptor in islets from *Ppar*α knockout mice [10]. A PPARα-dependent mechanism was also found to regulate the expression of the *Gipr* in beta cells by glucose and fat [22]. Treatment of Otsuka Long Evans Tokushima Fatty (OLETF) rats, an obese animal model of type 2 diabetes, with the PPARα agonist fenofibrate reduced the decline in beta cell mass and prevented the development of diabetes [23]. However, there appeared to be no additional glucose-lowering effect with the addition of fenofibrate to metformin therapy in humans [24, 25]. Additional studies will be required to determine whether metformin can increase incretin receptor expression in human beta cells and thereby bolster incretin action in a meaningful way.

Although there are undoubtedly more details to unravel regarding the mechanisms of action of metformin, the work by Maida et al. [10] extends previous findings to indicate that metformin can be regarded as an enhancer of GLP-1 secretion and possibly as a GLP-1 sensitiser, beyond its known biological functions (Fig. 1). Certainly, the addition of a DPP-4 inhibitor to metformin therapy can boost GLP-1 levels much higher than the addition of a sulfonylurea [26]. Clinical studies have also indicated that metformin alone can increase GLP-1 levels, via a mechanism distinct from DPP-4 inhibition, and that combination therapy has a complementary effect on GLP-1 concentrations [27]. These findings suggest that a mechanism similar to that observed in mice [10] is at work in humans and that combining metformin with DPP-4 inhibitors appears to be a rational way of enhancing GLP-1 signalling in pancreatic beta cells. However, metformin-induced enhancement of incretin action does not appear to be a major mechanism by which metformin lowers blood glucose. Despite increased GLP-1 levels and incretin receptor expression on beta cells, the lower glucose levels achieved with metformin treatment were not associated with increased insulin levels [10]. Even more compelling is the finding that metformin essentially appeared to be as potent in lowering blood glucose levels in incretin receptor knockout mice as it did in wild-type mice. Given that the glucose-lowering effect of metformin is so strong and is independent of incretin signalling, it might be difficult to detect the beneficial effect of metformin on the incretin axis in human studies. Nonetheless, it would be interesting to examine whether or not metformin is able to reverse the decreased sensitivity of pancreatic beta cells to the insulinotropic effects of incretins associated with genetic polymorphisms in *TCF7L2* [28–30] and *WFS1* [31]. It just may be that there are still unappreciated benefits to the old drug, metformin.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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