Stimulatory effect of imeglimin on incretin secretion

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学 位 論 文 の 内 容 要 旨

Stimulatory effect of imeglimin on incretin secretion

イメグリミンによるインクレチン分泌促進作用

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Introduction

Imeglimin is a newly launched anti-diabetic drug structurally related to metformin. Despite the structural similarity, imeglimin augments glucose-stimulated insulin secretion (GSIS), which the action metformin does not possess. The mechanism of how imeglimin enhances GSIS remains ambiguous, however. Given that the incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), also enhance GSIS, we examined whether one of these hormones are involved in the pharmacological actions of imeglimin.

Method

We examined plasma insulin and incretin levels during an oral glucose tolerance test (OGTT) performed with C57BL/6JJcl (B6) and KK-Ay/TaJcl (KK-Ay) mice after a single-dose of imeglimin alone or in combination with sitagliptin (a DPP-4 inhibitor). We also investigated whether imeglimin had an additive effect on the enhancement of GSIS by GIP or GLP-1 in mouse islets. The effect of the GLP-1 receptor antagonist Exendin-9 on the glucose-lowering and insulin-stimulating actions of imeglimin has also been examined. Moreover, the acute effects of imeglimin on blood glucose and plasma insulin levels in *Glp1r KO* mice (GLP-1 receptor knockout mice on the C57BL/6

genetic background) was also involved in this study.

RESULTS

To provide insight into the mechanisms underlying the antidiabetic action of imeglimin, we first investigated the acute effects of the imeglimin in B6 mice and KK-Ay mice. OGTT was performed on both mice with a 6-h fasting and 1-h drug preloading. We found that imeglimin decreased and increased blood glucose and plasma insulin levels, respectively, in both mice, and increased plasma GIP and GLP-1 levels in KK-Ay mice and GLP-1 levels in B6 mice.

Given that imeglimin was found to increase the plasma incretin concentration in KK-Ay mice, we next investigated the effects of the combination of imeglimin and a DPP-4 inhibitor sitagliptin on blood glucose and plasma insulin and incretin levels in these mice. During the OGTT, the combination of the two drugs reduced blood glucose levels to a significantly greater extent compared with either drug alone. The plasma concentration of insulin tended to be higher in imeglimin-treated mice, whereas sitagliptin had no substantial effect on insulin levels. However, combined treatment with the two drugs markedly increased plasma insulin levels compared with treatment with either drug alone. Plasma levels of GLP-1 tended to be increased in imeglimin-treated mice and sitagliptin-treated mice, and they were significantly higher in mice treated

with both drugs than in those treated with either drug alone. These results indicated that imeglimin and sitagliptin exerted synergistic effects on blood glucose, plasma insulin, and plasma GLP-1 levels.

We next investigated the effects of imeglimin and incretins on GSIS in pancreatic islets isolated from B6 mice. The results showed that imeglimin and GLP-1, but not GIP, additively enhanced GSIS in islets of B6 mice.

We next examined whether the GLP-1 receptor antagonist exendin-9 might influence the effects of imeglimin on blood glucose and plasma insulin levels during an OGTT. We found that blood glucose levels were significantly lower in KK-Ay mice treated with imeglimin, and this effect of imeglimin tended to be inhibited by exendin-9, which suggested that exendin-9 might partially attenuate the glucose-lowering effect of imeglimin. However, there was no difference between imeglimin alone and the combination of the two drugs in terms of increasing plasma insulin levels during the OGTT.

Finally, we investigated the effects of imeglimin on blood glucose and plasma insulin levels during an OGTT in *Glp1r* KO mice. Imeglimin significantly attenuated the increase in blood glucose levels in these mice to a similar extent as in B6 mice. The plasma levels of insulin tended to be increased by imeglimin treatment. Whereas these

results do not exclude a possible contribution of GLP-1 to the glucose-lowering effect of imeglimin, they implicate a mechanism independent of GLP-1.

DISCUSSION

We have shown that a single dose of imeglimin increased the plasma concentrations of GIP and GLP-1 in KK-Ay mice during an OGTT, and the combination of imeglimin and sitagliptin showed marked synergistic effects on the plasma levels of GLP-1 and insulin. Moreover, imeglimin and GLP-1 enhanced GSIS by isolated mouse islets in an additive manner. These results suggest that an imeglimin-induced increase in GLP-1 levels contributes to the promotion of insulin secretion by this drug, with this effect of imeglimin on GSIS being thought to play an important role in the antidiabetic action of the drug.

In summary, we have here shown that imeglimin increases plasma GLP-1 levels in mice, and that this action likely contributes at least in part to its stimulatory effect on insulin secretion. Whereas further study is required to validate the clinical relevance of this action of imeglimin, our current findings provide new insight into the pharmacological effects and clinical use of this new antidiabetic drug.

神戸大学大学院医学(系)研究科（博士課程）

論文審査の結果の要旨

受付番号	甲　3293　号	氏名	権　映月
論文題目 Title of Dissertation	Stimulatory effect of imeglimin on incretin secretion イメグリミンによるインクレチン分泌促進作用		
審査委員 Examiner	主査 Chief Examiner 副査 Vice-examiner 副査 Vice-examiner	坂口一彦 平田健一 野津寛大	

（要旨は１，０００字～２，０００字程度）

In this study, the candidate has investigated whether incretin hormones (GIP and GLP-1) might contribute to the pharmacological actions of imeglimin. Imeglimin is a new antidiabetic drug that lowers glucose primarily by amplifying glucose-stimulated insulin secretion. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide–1 (GLP-1) improves glucose tolerance by stimulating insulin secretion from pancreatic β-cells in a glucose-dependent manner, and its potential role in imeglimin action has been unknown.

The subjects in this study included C57BL/6JJcl (C57BL/6), KK-Ay/TaJcl (KK-Ay), or Glp*1r* KO mice. OGTT was performed after 6 hours of food deprivation, and the oral glucose load was 1.5 g/kg. Blood glucose and plasma insulin, GIP, and GLP-1 concentrations were measured during the OGTT after administration of a single dose of imeglimin with or without the dipeptidyl peptidase–4 inhibitor sitagliptin or the GLP-1 receptor antagonist exendin-9. The effects of imeglimin with or without GIP or GLP-1 on GSIS were examined in C57BL/6 mouse islets.

To provide insight into the mechanisms underlying the antidiabetic action of imeglimin, the candidate first investigated the acute effects of the drug in B6 mice and KK-Ay diabetic mice. Imeglimin lowered blood glucose and increased plasma insulin levels during an OGTT in both C57BL/6 and KK-Ay mice, whereas it also increased plasma GIP and GLP-1 levels in KK-Ay mice and GLP-1 levels in C57BL/6 mice. Based on this result, the candidate next examined the combination effect of imeglimin and dipeptidyl peptidase–4 inhibitor sitagliptin on KK-Ay mice. This combination reduced blood glucose and increased plasma insulin and GLP-1 levels during the OGTT in KK-Ay mice to a markedly greater extent than did either drug alone. The candidate also showed that imeglimin enhanced GSIS in an additive manner with GLP-1, but not with GIP, in mouse islets. To investigate the involvement of GLP-1 secretion on the hypoglycemic effect of imeglimin, the candidates studied the effect of the GLP-1 receptor antagonist exendin-9 combined with or without imeglimin on blood glucose during OGTT in KK-Ay mice, and the results suggested that exendin-9 had only a minor inhibitory effect on the glucose-lowering action of imeglimin. OGTT data collected in GLP-1 receptor knockout (Glp*1r* KO) mice of C57BL/6 genetic background showed that imeglimin significantly attenuated the increase in blood glucose levels in these mice after initiation of the test as well as reduced the AUC. The plasma insulin levels tended to be increased by imeglimin treatment, but this effect was not statistically significant. Whereas these results do not exclude a possible contribution of GLP-1 to the glucose-lowering effect of imeglimin, they implicate a mechanism independent of GLP-1.

This study has shown that imeglimin increases plasma GLP-1 levels in mice, and this action likely contribute at least in part to its stimulatory effect on insulin secretion. The current findings provide new insight into the pharmacological effects and clinical use of this new antidiabetic drug.

The candidate, having completed studies on imeglimin, with a specialty in GLP-1 activation, and having advanced the field of knowledge in the area of pharmaco-diabetology, is hereby recognized as having qualified for the degree of Ph.D.(Medicine).