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Isoferulic acid attenuates methylglyoxal-induced apoptosis in INS-1 rat pancreatic β-cell through mitochondrial survival pathways and increasing glyoxalase-1 activity

Aramsri Meeprom[a,c], Catherine B Chan[b], Weerachat Sompong[c], Sirichai Adisakwattana[c,*]

[a] Program in Clinical Biochemistry and Molecular Medicine, Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, 10330, Thailand
[b] Departments of Physiology and Agricultural, Food and Nutritional Sciences, University of Alberta, Edmonton, Alberta T6G 2R3, Canada
[c] Department of Nutrition and Dietetics, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, 10330, Thailand

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ABSTRACT

Methylglyoxal (MG) is a reactive precursor to advanced glycation end-products (AGEs), which exert deleterious effects on cells and tissues. MG also causes pancreatic β-cell dysfunction and apoptosis. Isoferulic acid (IFA), a naturally occurring cinnamic acid derivative, is considered to be an antiglycating agent. However, the effect of IFA on MG-induced pancreatic β-cell dysfunction remains unknown. The objective of this study was to determine the protective effect of IFA against MG-induced mitochrondrial dysfunction and apoptosis in INS-1 pancreatic β-cells. The results showed that pretreatment of INS-1 cells with 100 μM IFA for 48 h prevented MG-induced decrease in cell viability and impairment of glucose-stimulated insulin secretion (GSIS). In addition, 100 μM IFA pretreatment also decreased MG-induced generation of reactive oxygen species (ROS) and upregulation of mitochondrial uncoupling protein 2 (Ucp2) mRNA expression. Furthermore, IFA pretreatment reduced MG-induced increase in caspase-3 activity, suggesting a reduction of apoptotic cell death. IFA (50–100 μM) itself markedly increased the activity of glyoxalase 1 (GLO1), a major enzyme for the detoxification of MG. The results showed that 100 μM IFA protected MG-induced loss of GLO1 activity in INS-1 cells. These findings suggest that IFA pretreatment attenuates MG-induced dysfunction and apoptosis in INS-1 pancreatic β-cells through mitochondrial survival pathway and increasing GLO1 activity.

1. Introduction

Methylglyoxal (MG), a highly reactive intermediate metabolite, is normally produced from basal carbohydrate, lipid, and protein metabolism [1]. It has been shown that MG production is highly increased in hyperglycemic conditions such as diabetes mellitus [2]. MG directly reacts with lysine and arginine residues of proteins to produce a complex cascade of reactions, resulting in the formation of advanced glycation end-products (AGEs) [1]. Several studies demonstrated that the accumulation of AGEs in the tissues is a causative factor to induce the production of pro-inflammatory mediator and the generation of reactive oxygen species (ROS), which contribute to damage of cellular components including proteins [3] and DNA [4,5]. In addition to the formation of AGEs, MG has also cytotoxic properties especially apparent in pancreatic β-cells [6]. Recent findings indicate that MG induces mitochondrial dysfunction by increasing oxidative stress, upregulating mitochondrial uncoupling protein 2 (UCP2), and suppressing the respiratory chain and ATP synthesis [7]. These alterations of mitochondrial function triggers cell apoptosis and impairs glucose-stimulated insulin secretion in pancreatic β-cells [7–9]. Impaired functions of pancreatic β-cells could promote the progression of diabetes and its complications [10]. Glyoxalase system is recognized as the major enzymes for the detoxification of MG in the cytosol of all cells. It has been revealed that increased glyoxalase 1 (GLO1) activity decreases cytotoxicity of MG and the formation of AGEs [11]. Therefore, attenuation of MG-induced cytotoxicity and mitochondrial alterations is a proposed target for protection of pancreatic β-cell apoptosis and dysfunction.

There is compelling evidence that dietary phytochemical compounds exhibit antiglycation activity in a number of experimental models [12,13]. Especially, cinnamic acid and its derivatives have received increasing attention in recent years due to their biological activities [12]. Isoferulic acid (IFA), a naturally occurring cinnamic acid, is a main active ingredient of the rhizoma of *Cimicifuga dahurica*.

* Corresponding author.
E-mail address: Sirichai.a@chula.ac.th (S. Adisakwattana).

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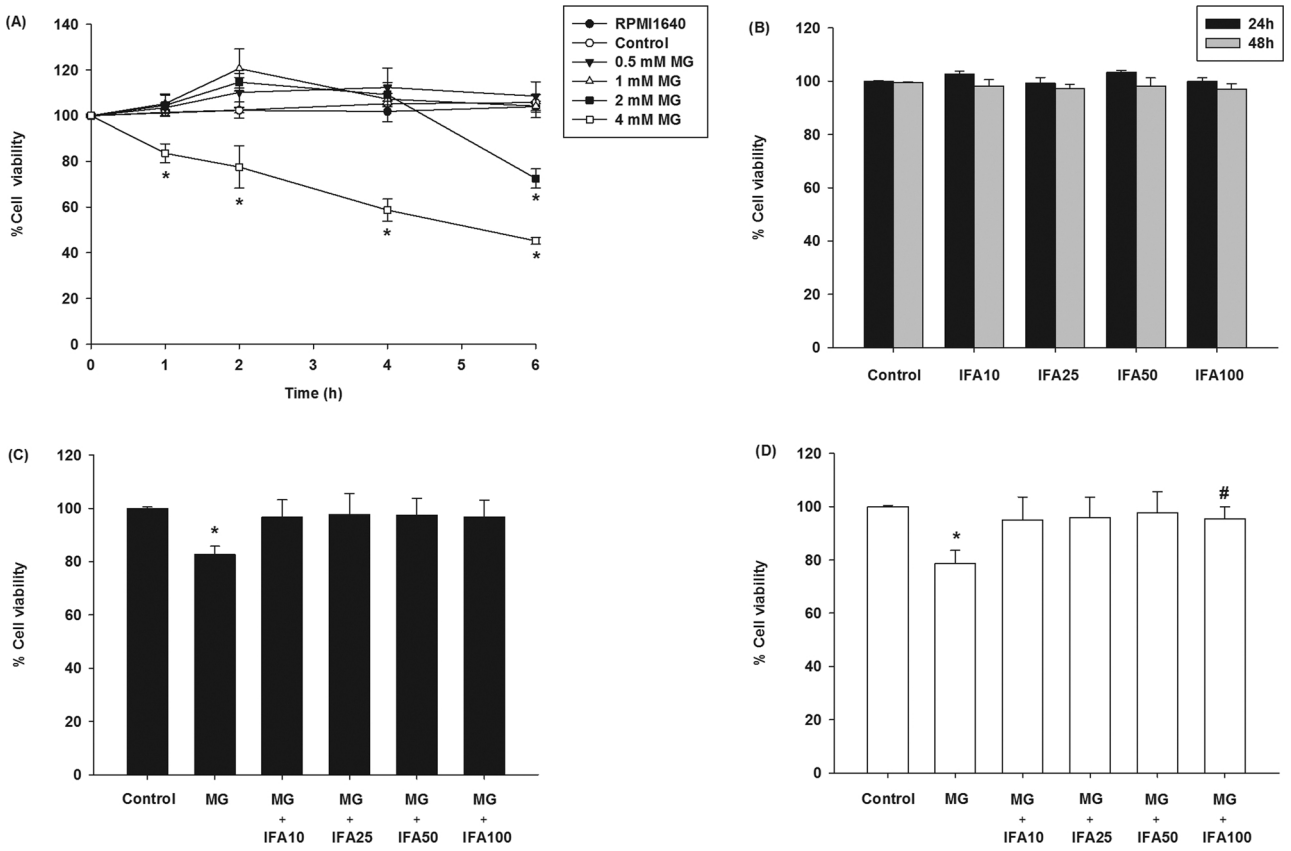

Fig. 1. (A) The viability of INS-1 cells treated with various concentrations of MG (0.5–4 mM) during 1–6 h. (B) The viability of INS-1 cells treated with various concentrations of IFA for 24 and 48 h. Effect of IFA pretreatment for 24 h (C) and 48 h (D) on the viability of INS-1 cells. INS-1 cells were pretreated with IFA for 24 or 48 h and then incubated with 2 mM MG for 6 h. The results are presented as mean ± SEM (n = 3). $^{*}P < 0.05$ compared to the control, $^{\#}P < 0.05$ compared to 2 mM MG.

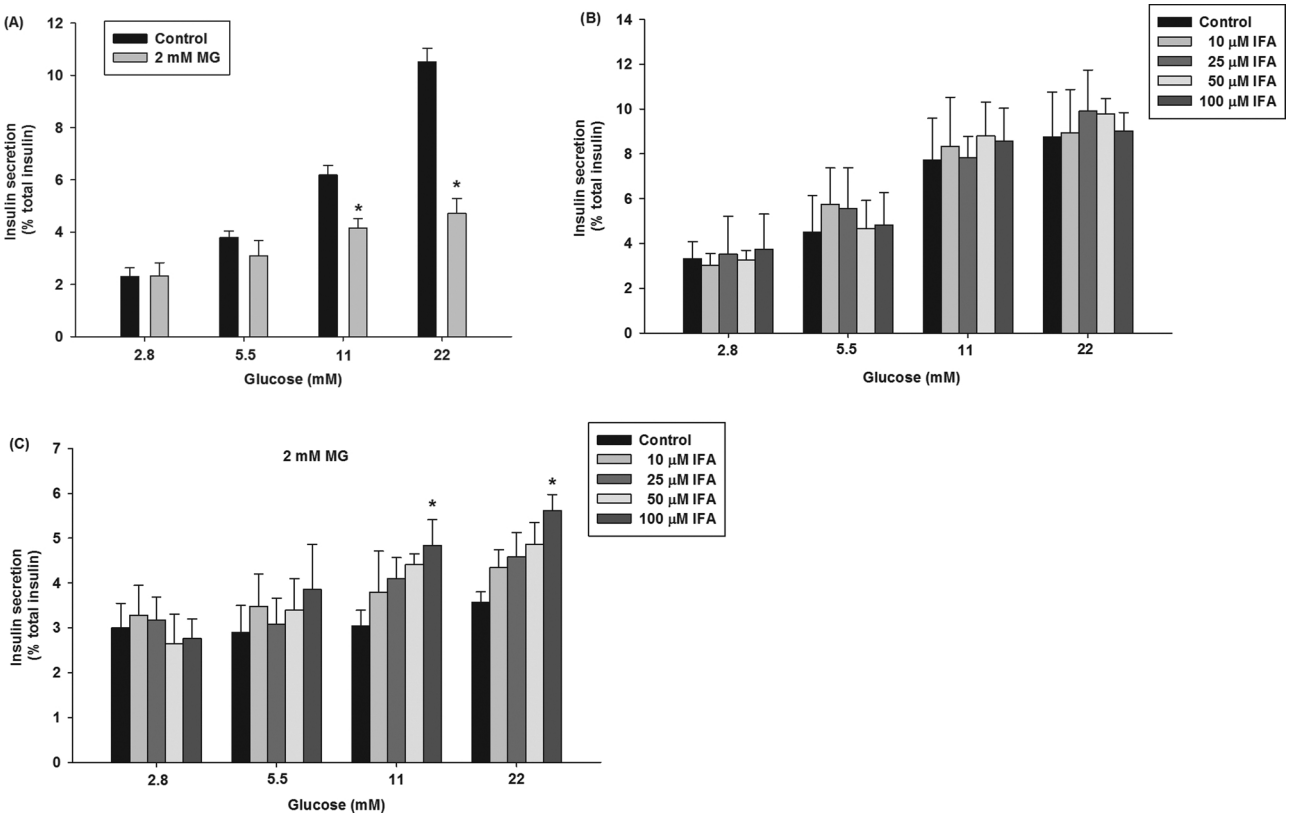

Fig. 2. (A) Glucose-stimulated insulin secretion (GSIS) of INS-1 cells treated with 2 mM MG for 2 h. (B) Effect of IFA pretreatment for 48 h on GSIS in INS-1 cells for 2 h. (C) Effect of IFA pretreatment for 48 h on GSIS in INS-1 cells treated with 2 mM MG for 2 h. The results are presented as mean ± SEM (n = 3). $^{*}P < 0.05$ compared to the control.