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Des-aspartate-angiotensin-I and angiotensin IV improve glucose tolerance and insulin signalling in diet-induced hyperglycaemic mice

Yong-Chiat Wong [a], Meng-Kwoon Sim [a,*], Kok-Onn Lee [b]

[a] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[b] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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ABSTRACT

Although clinical studies suggested that blockade of the renin-angiotensin system may prevent diabetes, the mechanism is uncertain. As a follow-up to an earlier study, we investigated how des-aspartate-angiotensin-1 (DAA-1) and its metabolite, angiotensin IV (Ang-IV) improved glucose tolerance in diet-induced hyperglycaemic mice. Male C57BL/6J mice were fed a high-fat-high-sucrose (HFD) or normal (ND) diet for 52 weeks. HFD animals were orally administered either DAA-I (600 nmol/kg/day), Ang-IV (400 nmol/kg/day) or distilled water. Body weight, blood glucose and insulin were measured fortnightly. Inflammatory and insulin signalling transducers that are implicated in hyperglycaemia were analyzed in skeletal muscles at 52 weeks. HFD animals developed hyperglycemia, hyperinsulinemia and obesity. DAA-I and Ang-IV improved glucose tolerance but had no effect on hyperinsulinemia and obesity. Skeletal muscles of HFD animals showed increased level of ROS, gp91 of NADPH oxidase, pJNK and AT_1R-JAK-2-IRS-1 complex. Both DAA-I and Ang-IV attenuated these increases. Insulin-induced activation of IR, IRS-1, IRS-1-PI3K coupling, phosphorylation of Akt, and GLUT4 translocation were attenuated in skeletal muscles of HFD animals. The attenuation was significantly ameliorated in DAA-I-treated HFD animals. In corresponding Ang-IV treated animals, insulin induced IRAP and PI3K interaction, activation of pAkt and GLUT4 translocation, but no corresponding activation of IR, IRS-1 and IRS-1-PI3 K coupling were observed. DAA-I and Ang-IV improved glucose tolerance, insulin signalling, and para-inflammatory processes linked to hyperglycaemia. DAA-I acts via the angiotensin AT_1 receptor and activates the insulin pathway. Ang-IV acts via IRAP, which couples PI3K and activates the later part of the insulin pathway.
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1. Introduction

Angiotensin II (Ang-II) is involved in the pathogenesis of diet-induced hypertension and insulin resistance [1–3]. The angiotensin AT_1 receptor has been shown to couple components of insulin signalling pathway via JAK2 to form JAK/IRS-1/PI3K, and to activate JNK. These two actions result in inhibitory serine phosphorylation of key elements of the insulin-signalling pathway [4–6]. Consistent with these findings, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been reported to improve insulin resistance in type 2 diabetics [7–9]. Inhibition of the renin angiotensin system (RAS) in the LIFE trial was also associated with a reduction in the risk of new-onset diabetes [10]. Similar association was also seen in the CHARM [11] and VALUE [12] studies. These large randomized clinical trials show a possible causal relationship between increase in RAS activity and diabetes. Tikellis et al. [13] investigated the specific effects of RAS blockade on pancreatic islet structure and function in diabetic rats. They showed that Zucker rats exhibited increased intraislet expression of various components of the RAS in association with fibrosis, apoptosis, and oxidative stress; and these were attenuated after treatment with perindopril or irbesartan. Besides blockade of the RAS, treatment of diabetic animals with angiotensins that exert biological actions opposing those of angiotensin II was also beneficial. Angiotensin-(1-7) antagonizes the actions of angiotensin II [14,15], and in this respect the heptapeptide has been shown to reduce cardiovascular events associated with oxidative stress in diabetic animals [14–16]. Des-aspartate-angiotensin I (DAA-I), a metabolite of angiotensin I that counteracts several actions of Ang-II [17–20] was recently shown to exert hypoglycaemic action by enhancing insulin-induced GLUT4 translocation in type 2 diabetic KKAy mice and GK rats [21]. The effect of angiotensin IV (Ang-IV) on glucose regulation has also been of interest following the identification of

Abbreviations: Akt, protein kinase B; Ang-II, angiotensin II; Ang-IV, angiotensin IV; DAA-I, des-aspartate-angiotensin I; HFD, high-fat-high-sucrose diet; IR, insulin receptor; IRAP, insulin-related aminopeptidase; JAK, Janus kinase; JNK, c-Jun N-terminal kinases; ND, normal diet; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species.

* Corresponding author. Tel.: +65 6516 3268; fax: +65 6873 7690.
E-mail address: phcsimmk@nus.edu.sg (M.-K. Sim).

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insulin-regulated aminopeptidase (IRAP) as the AT_4 receptor that is linked to the pathogenesis of T2DM [22]. IRAP is known to be involved in GLUT4 trafficking and insulin-stimulated glucose uptake into insulin-responsive cells [23,24]. Although IRAP co-translocates with GLUT4 to the cells surface in response to insulin stimulation in adipocytes, cardiomyocytes and skeletal muscle cells [25–27], the ability of IRAP to mediate the actions of Ang-IV and its role in insulin action in peripheral tissues remains largely unknown. On the basis that insulin resistance in skeletal muscle is a hallmark of type 2 diabetes [28–31], the mechanism of improved glucose tolerance of DAA-I and Ang-IV in the skeletal muscles of diet-induced hyperglycaemic mice was investigated in the present study.

2. Materials and methods

2.1. Antibodies and chemicals

Anti-gp91phox, anti-phospho-JNK, anti-insulin Rα, anti-phospho-IRS-1 (Ser307), anti-phospho-Tyrosine, anti-IRS-1, anti-PI 3-kinase p85α, anti-Akt, anti-GLUT4, anti-phospho-Serine, anti-AT_1R, anti-JAK2, goat anti-mouse IgG-HRP, goat anti-rabbit IgG-HRP, donkey anti-goat IgG-HRP, goat anti-mouse IgM-HRP antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Anti-JNK 1/2 antibody was obtained from BD Pharmingen (San Diego, CA). Anti-phospho-Akt (Ser473) antibody was purchased from Cell Signalling Technology (Danvers, MA). Anti-IRAP antibody was purchased from Alpha Diagnostic (San Antonio, TX). Anti-β-actin antibody and divalinal angiotensin IV were purchased from Sigma Aldrich (St. Louis, MO). DAA-I and Ang-IV were purchased from Bachem AG (Bubendorf, Switzerland). Indomethacin was purchased from Cayman Chemical Company (Ann Arbor, MI). Losartan was a gift from Merck & Co., Inc. (Whitehouse Station, NJ).

2.2. Animals

Five- to 6-week-old male C57BL/6J male mice were purchased from the National University of Singapore Centre for Animals Resources. The animals were housed in temperature controlled room at 25 ± 1 °C with lighting from 0700 to 1900 h daily. The use of animals in this study was approved by Institutional Animal Care and Use Committee of National University of Singapore.

2.3. Diet

The animals received either normal diet (ND, Specialty Feeds, Australia) or high-fat high-sucrose diet (HFD, Specialty Feeds, Australia) and water *ad libitum*. On a caloric base, the ND consisted of 19% protein, 12% carbohydrates and 4.6% fat (total 13.5 kJ/g), whereas the HFD consisted of 19% protein, 42% carbohydrates and 23% fat (total 20 kJ/g).

2.4. Oral administration of angiotensin peptides

The animals were randomly assigned into groups of 10 animals as follows:

ND control	mice fed with ND plus oral administration of 0.1 ml drinking water/day.
HFD control	mice fed with HFD plus oral administration of 0.1 ml drinking water/day.
HFD+DAA-I (0)	mice fed with HFD plus oral administration of 600 nmol/kg/day DAA-I starting from 0th week of the diet regime.
HFD+Ang-IV (0)	mice fed with HFD plus oral administration of 400 nmol/kg/day Ang-IV starting from 0th week of the diet regime.
HFD+DAA-I (24)	mice fed with HFD plus oral administration of 600 nmol/kg/day DAA-I starting from 24th week of the diet regime.
HFD+Ang-IV (24)	mice fed with HFD plus oral administration of 400 nmol/kg/day Ang-IV starting from 24th week of the diet regime.

The dose of 600 nmol/kg DAA-I was shown to exert maximum hypoglycaemic effect in diabetic animals in a previous study [21], and a preliminary study showed that 400 nmol/kg Ang-IV exerted maximal glucose lowering effect (unpublished findings). Animals were administered 0.1 ml solution of either DAA-I, Ang-IV or distilled water by oral gavage. The food intake of the animals was determined every 4 weeks for a duration of 48 weeks. The calculation of the energy consumed was based on the weight of the food pellet consumed by the animals for a 24-h period. The weight of food pellet consumed was multiplied by the amount of digestible energy (given by the manufacturer) divided by the weight of the animals, and the energy value was expressed as MJ/g/day. After 52 weeks of treatment, the animals were then subjected to acute insulin stimulation and sacrificed for various molecular studies. With this duration of HFD treatment, the prophylactic actions of both angiotensin peptides (concurrent treatment from 0 week) as well as their actions on fully developed hyperglycaemia (concurrent treatment from 24 weeks) could be studied.

2.5. Intraperitoneal administration of losartan, divalinal-Ang-IV, and indomethacin

Five to 6-week old animals fed on a ND and water *ad libitum* were orally administered either DAA-I (600 nmol/kg/day), Ang-IV (400 nmol/kg/day) or vehicle (water) for up to 6 weeks. DAA-I-treated animals were concurrently administered one of the following by intraperitonal injection: losartan (50 nmol/kg/day), divalinal-Ang-IV (300 nmol/kg/day), indomethacin (200 nmol/kg/day). Ang-IV-treated animals were similarly administered losartan or divalinal Ang-IV. Control animals were administered either losartan, divalinal-Ang-IV, or indomethacin. Indomethacin powder was directly dissolved in 0.1 M warm Na_2CO_3 in concentration of 0.1 mg/ml and subsequently diluted to appropriate concentration in PBS (pH 7.2).

2.6. Oral glucose tolerance test (OGTT) and serum insulin determination

At every 4 weeks, the animals were fasted overnight and the weight of individual animals was recorded prior to an oral administration of 2 g/kg glucose solution. Blood was taken from the orbital sinus (10 μl) of each animal immediately before glucose administration, and at 30, 60, and 120 min after glucose administration. The blood was allowed to clot and the serum assayed for glucose and insulin concentration using commercial glucose reagent and insulin kits from Thermo Electron Corp (Victoria, Australia) and Crystal Chem Inc (Downers Grove, IL), respectively.

2.7. Correlation of serum glucose and insulin with insulin resistance

The whole-body insulin sensitivity was calculated based on an equation defined as an index of whole body insulin sensitivity [10,000/square root of (fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT)]. This index has been shown to correlate with the rate of whole-body glucose disposal during the euglycemic insulin clamp [32].

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