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Research Article

Comparison of Sitagliptin with Vildagliptin's effects on Mitochondrial Activity, Heart Rate Variability, and Cardiac Performance in Obese Insulin-Resistant Rats

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Abstract

Context and Objective: It has been demonstrated that a prolonged high-fat diet (HFD) can lead to insulin resistance, which is typified by hyperinsulinemia and metabolic inflexibility. Heart failure, cardiac mitochondrial dysfunction, and cardiac sympathovagal imbalance are all linked to insulin resistance. Oral anti-diabetic medications called sitagliptin and vildagliptin, which block dipeptidyl peptidase-4 (DPP-4), are frequently administered to individuals suffering from cardiovascular disease. Thus, using a mouse model of insulin resistance, we aimed to investigate the effects of sitagliptin and vildagliptin in this work. Method of Experimentation: Male For a period of 12 weeks, 180–200 g Wistar rats were fed either an HFD (59% energy from fat) or a regular diet (20% energy from fat). After that, these rats were split up into three subgroups and given either vehicle for an additional 21 days, sitagliptin (30 mg/kg/day-1), vildagliptin (3 mg/kg−1 day−1), or both days. Heart rate variability (HRV), cardiac function, oxidative stress, metabolic parameters, and cardiac mitochondrial function were all measured Important Findings: In rats fed a high-fat diet (HFD), they developed insulin resistance, which was manifested as a decrease in high-density lipoprotein (HDL) and an increase in body weight, plasma insulin, total cholesterol, and oxidative stress levels. Furthermore, HFD rats showed evidence of cardiac dysfunction, decreased HRV, cardiac mitochondrial dysfunction, and alterations in cardiac mitochondrial morphology. Vildagliptin and sitagliptin both raised HDL levels while lowering plasma insulin, total cholesterol, and oxidative stress. Additionally, sitagliptin and vildagliptin fully restored HRV and reduced cardiac dysfunction as well as cardiac mitochondrial dysfunction Conclusions and Significance: In obese insulin-resistant rats, vildagliptin and sitagliptin both had comparable cardioprotective effects.

Keywords: sitagliptin; vildagliptin; high-fat diet; insulin resistance; cardiac function

Abbreviations:

DBP, diastolic BP; DPP-4, dipeptidyl peptidase-4; EDP, end-diastolic pressure; ESP, end-systolic pressure; FFT, fast Fourier transform; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HF, high-frequency; HFD, high-fat diet; HFDSi, high-fat diet group treated with sitagliptin; HFDV, high-fat diet group treated with vehicle; HFDVil, high-fat diet group treated with vildagliptin; HOMA, homeostasis model assessment; HR, heart rate; HRV, heart rate variability; JC-1, 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetra ethylbenzimidazolcarbocyanine iodide; LDL, low-density lipoprotein; LF, low-frequency; MDA, malondialdehyde; ND, normal diet; NDSi, normal-diet group treated with sitagliptin; NDV, normal-diet group treated with vehicle; NDVil, normal-diet group treated with vildagliptin; ROS, reactive oxygen species; SBP, systolic BP; SV, stroke volume; SW, stroke work; TBA, thiobarbituric acid; TBARS, thiobarbituric acid reactive substances; VLDL, very low-density lipoprotein; VLF, very low-frequency.

Introduction :

Insulin resistance has been linked to long-term high-fat diet (HFD) intake (Pratchayasakul et al., 2011; Pipatpiboon et al., 2012). Heart malfunction (Ouwens et al., 2005), cardiac mitochondrial dysfunction (Dong et al., 2007), and cardiac sympathovagal dysregulation (Pongchaidecha et al., 2009) are all at risk due to insulin resistance. Oral anti-diabetic medications called dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin and vildagliptin, block the DPP-4 enzyme, which prolongs the action of the glucagon-like peptidase-1 (GLP-1) hormone. Intestinal L-cells release the incretin hormone GLP-1. According to a number of research (Buse et al., 2004; Bose et al., 2005; Poornima et al., 2008), GLP-1 has positive effects that lower plasma glucose levels and improve heart function in human tests and animal models. Additionally, DPP-4 inhibitors demonstrate a positive impact on cardiac and metabolic indices (Ahren et al., 2004; Lenski et al., 2011; Apaijai et al., 2012). According to research conducted on animals and

humans, sitagliptin and vildagliptin can lower blood glucose levels and raise plasma insulin in type 2 diabetes models (Mari et al., 2005; Tremblay et al., 2011). Additionally, sitagliptin reduces cardiac fibrosis in diabetic mice (Lenski et al., 2011) and vildagliptin exhibits a cardioprotective effect in the hearts of swine (Chinda et al., 2012) and insulin-resistant rats (Apaijai et al., 2012). While research has been done on the effects of sitagliptin and vildagliptin, two DPP-4 inhibitors, on metabolic parameters, cardiac function, and mitochondrial function in HFD-induced insulin-resistant rats, it is yet unknown how these two drugs compare. The purpose of this investigation was to ascertain how long-term HFD consumption-induced insulin-resistant rats respond to vildagliptin and sitagliptin in terms of metabolic parameters, oxidative stress levels, heart rate variability (HRV), cardiac function, cardiac mitochondrial function, and cardiac mitochondrial morphology. In HFD-induced insulin-resistant rats, we predicted that vildagliptin and sitagliptin would enhance metabolic parameters, avoid an increase in oxidative stress levels, maintain HRV and cardiac function, and protect cardiac mitochondrial function.

Procedures

Diet and animals

provided thirty-six male Wistar rats weighing between 180 and 200 g. The temperature in the rats' quarters was kept at a constant 25°C with a 12-hour light/dark cycle. After a seven-day period for acclimation, the rats were split into two groups: the normal-diet (ND) group received a typical laboratory pelleted food with 20% energy from fat, while the high-fat diet (HFD) group was fed a diet with 59% energy from fat. The rats were given food in their (Pratchayasakul et al., 2011; Apaijai et al., 2012; Pipatpiboon et al., 2012) their corresponding diets for a duration of 12 weeks. Three treatment groups (n = 6/group) were created from each diet group. These groups included vildagliptin (3 mg kg−1·day−1; Gulfvus, Novartis, Bangkok, Thailand; Burkey et al., 2005; Apaijai et al., 2012), sitagliptin (30 mg kg−1·day−1; Januvia, MSD, Bangkok, Thailand; Chen et al., 2011), and vehicle (0.9% normal saline solution in an equal volume). These concentrations were selected because prior research (Burkey et al., 2005; Chen et al., 2011) demonstrated their

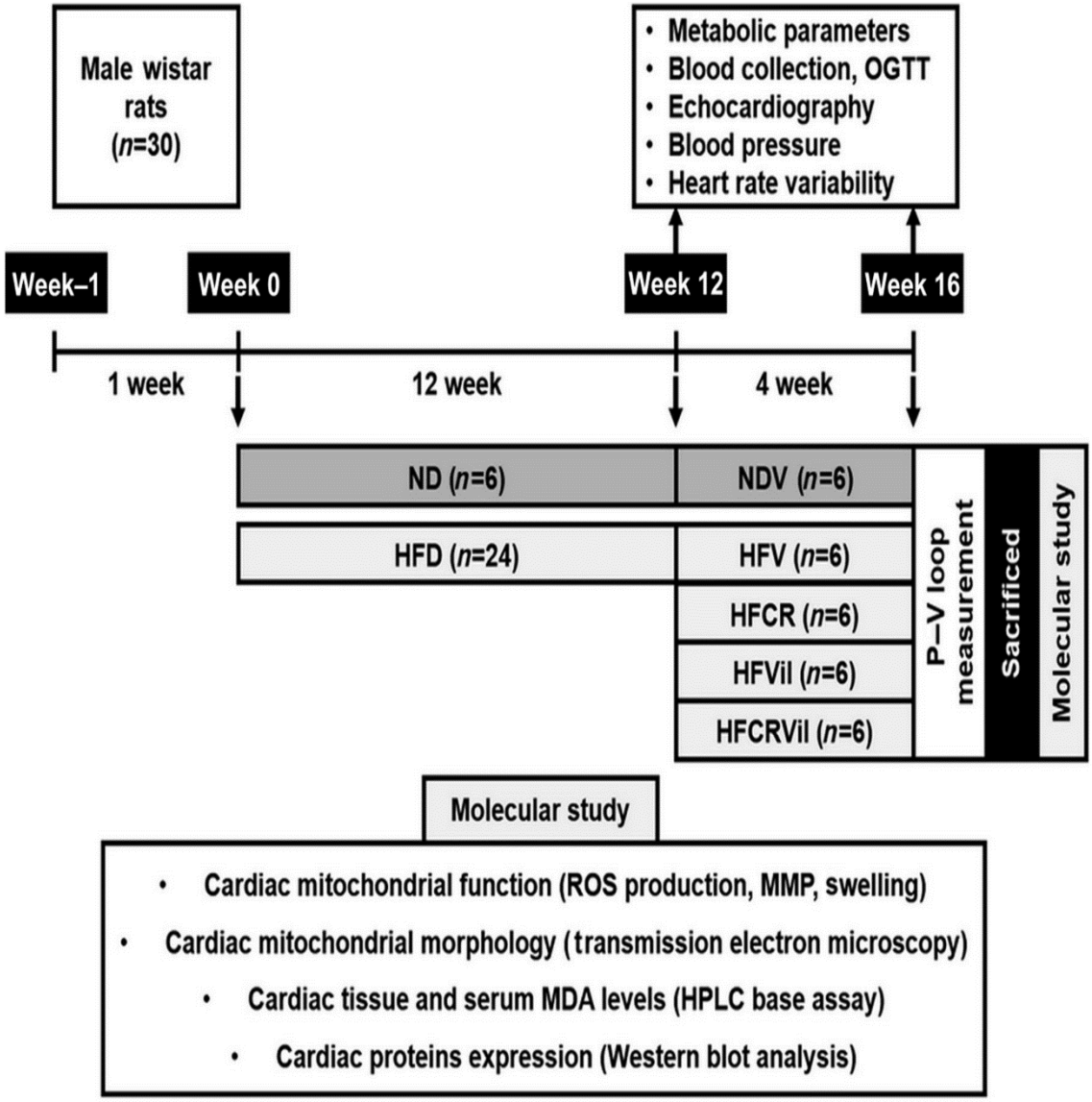

Figure 1: The experimental protocol of the study. HFCR, high-fat diet treated with CR diet; HFCRVil, high-fat diet treated with CR diet and vildagliptin; HFD, high-fat diet; HFV, high-fat diet treated with vehicle; HFVil, high-fat diet treated with vildagliptin; HPLC, high-performance liquid chromatography; MDA, Malondialdehyde; MMP, mitochondrial membrane potential; ND, normal diet; NDV, normal diet treated with vehicle; OGTT, oral glucose tolerance test; P–V loop, pressure–volume loop; ROS, reactive oxygen species.

ability to improve insulin sensitivity. For 21 days, rats were fed via gavage. Weekly food intake and body weight were noted. At weeks 0 through 12, blood samples were taken from the tail vein, and after fulfillment of the course of treatment. After being separated, the plasma was frozen at -85°C until it was needed. At the baseline (week 0), week 4, week 8, week 12, and post-treatment, HRV was measured. The pressure-volume catheter was utilized to ascertain the parameters of cardiac function (Scisence Inc., ON, Canada; Apaijai et al., 2012). Following the completion of the cardiac function investigation, the heart was quickly removed, and the levels of cardiac malondialdehyde (MDA) and cardiac mitochondria were measured in the left ventricular tissue (Apaijai et al., 2012).

Calculating the metabolic parameters

A commercial colorimetric assay kit (Biotech, Bangkok, Thailand) was used to measure the levels of total cholesterol and plasma glucose (Pipatpiboon et al., 2012). A commercial colorimetric assay kit was utilized to assess the levels of plasma high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) (Biovision; Singh et al., 2008; Milpitas, CA, USA). The sandwich ELISA kit (LINCO Research, St. Charles, MO, USA; Pratchayasakul et al., 2011; Pipatpiboon et al., 2012) was used to measure plasma insulin levels. Insulin resistance was evaluated using a mathematical model called the homeostasis model assessment (HOMA) index. The fasting plasma insulin concentration and glucose levels are used to compute the HOMA index. Higher levels of insulin resistance are indicated by higher HOMA index values (Pratchayasakul et al., 2011; Pipatpiboon et al., 2012).

Measuring the levels of MDA in the heart and plasma

Using an HPLC-based assay (Thermo Scientific, Bangkok, Thailand; Apaijai et al., 2012), the levels of MDA in plasma and the heart were measured. To create TBA reactive compounds (TBARS), plasma and cardiac MDA were combined with H3PO4 and thiobarbituric acid (TBA) According to Apijai et al. (2012), the concentration of TBARS in the plasma and heart was obtained using a standard curve and was reported as being equal to the concentration of MDA. All conscious rats had their HRV Lead II ECG measured using a PowerLab (ADInstruments, Colorado Springs, CO, USA) that was set up using the Chart 5.0 software. Each rat's ECG was recorded for 20 minutes. Figures 1A and 1 depict the stable ECG trace and the connection between the RR interval and the beat numbers (Tachogram), respectively. The fast Fourier transform (FFT) algorithm was used to derive the power spectra of the RR interval variability (Chattipakorn et al., 2007; Pongchaidecha et al., 2009; Apaijai et al., 2012; Kumfu et al., 2012). High-frequency (HF; 0.6–3) components were identified as the three main oscillatory components. low-frequency (LF; 0.2–0.6 Hz), very low-frequency (VLF; < 0.2 Hz), and high-frequency (HF; –3 Hz) bands. The power spectral density function's corresponding section was utilized to calculate the integrals for each spectral component, which were then displayed in the absolute unit (ms2). LF and HF were expressed as normalized units by dividing it by the total power minus VLF in order to reduce the impact of changes in total power on the LF and HF bands (Chattipakorn et al., 2007; Incharoen et al., 2007). The MATLAB software was used to analyze the LF (0.2–0.6 Hz) and HF (0.6–3 Hz) ratios (Pongchaidecha et al., 2009; Apaijai et al., 2012). The sympathovagal balance index is thought to be the LF/HF ratio (Chattipakorn et al., 2007; Kumfu et al., 2012). A higher LF/HF ratio suggested a lower HRV (Apaijai et al., 2012).

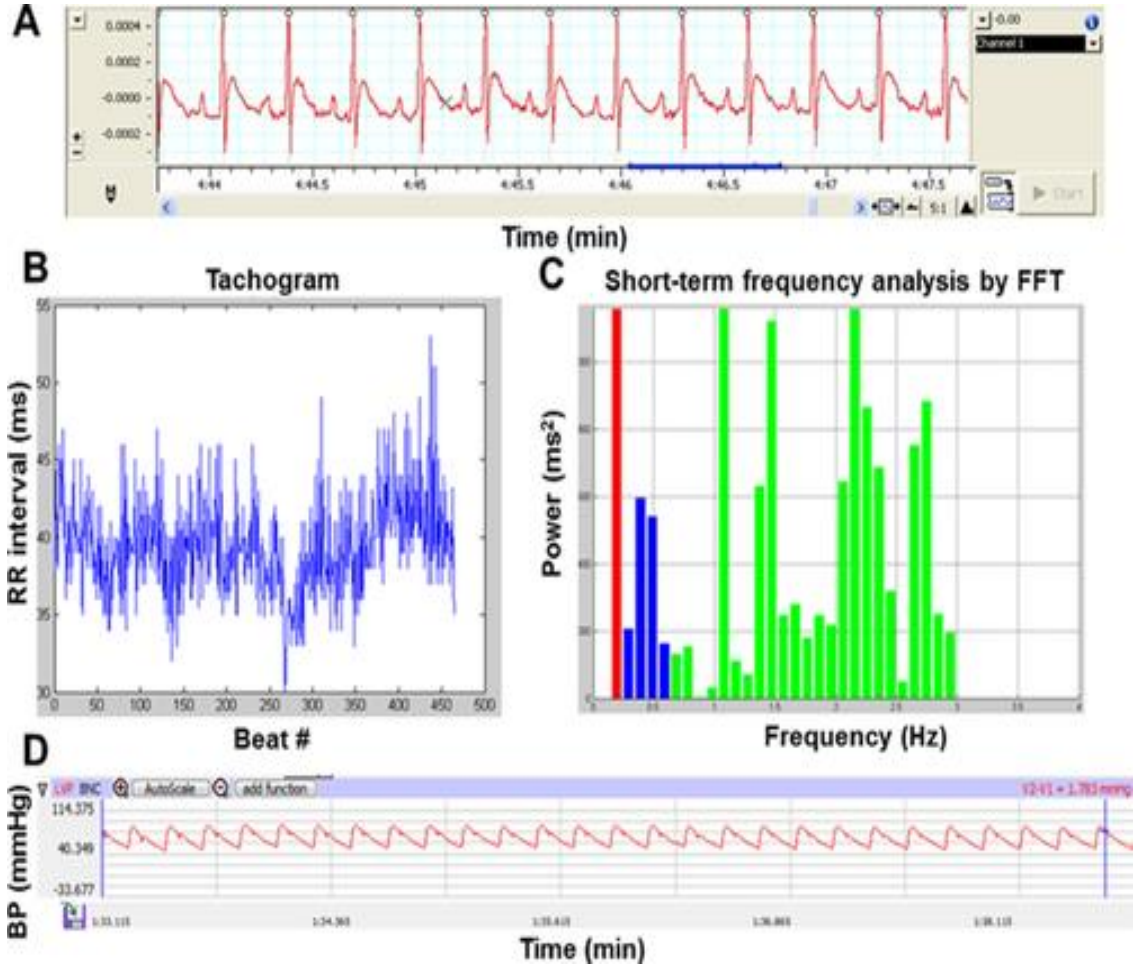

Figure 2: Representative figure of stable ECG trace (A), The RR interval and the beat numbers (Tachogram) (B), Power spectra of RR interval variability (C), and stable BP trace (D). The different colors in panel C represent the different frequency intervals for VLF, LF and HF for HRV analysis.

Heart performance

Rats were put to sleep by intramuscular injections of Xylazine (0.15 mg/kg; Laboratorios Calier, Barcelona, Spain) and Zoletil (50 mg/kg; Virbac Laboratories, Carros, France). Rats underwent tracheostomy and were ventilated using ambient air. A pressure–volume (P–V) catheter was placed after the right carotid artery was located. During the P-V loop measurement, the carotid artery was used to measure the diastolic blood pressure (DBP) and systolic blood pressure (SBP) (Figure 1D). After that, the catheter was inserted into the left ventricle. After giving the rats five minutes to settle, data were collected for twenty minutes. An analytical program was used to determine the cardiac function parameters, which included heart rate (HR), stroke work (SW), stroke volume (SV), maximum and minimum dP/dt (±dP/dt), end-systolic and diastolic pressure (ESP and EDP), and stroke work (SW) (Dover, New Hampshire, USA: Labscribe) (Apaijai et al., 2012; Kumfu et al., 2012).

Separation of cardiac mitochondria and assessment of mitochondrial function

The procedure previously outlined for cardiac mitochondrial isolation was followed (Thummasorn et al., 2011; Chinda et al., 2012). Every rat had its heart quickly removed after being infused with regular saline solution. Using an ice-cold buffer containing 300 mM sucrose, 5 mM N-[tris(hydroxymethyl)methyl]-2-aminoethanesulfonic sodium salt, and 0.2 mM EGTA, the left ventricular tissue was minced and homogenized. For five minutes, the homogenate was centrifuged at 800 g. After that, the supernatant was gathered and centrifuged for five minutes at 8800 g. The pellet was again suspended in respiration buffer, which contained 5 mM KH2PO4, 10 mM HEPES, 100 mM KCl, and 50 mM sucrose. In this study, the function of the heart's mitochondria, observed as changes in the heart mitochondrial membrane potential, the formation of reactive oxygen species (ROS), and the measurement of cardiac mitochondrial swelling. The formation of ROS in cardiac mitochondria was assessed by subjecting them to a 20-minute incubation period at 25°C with 2-μM 2-chloroserine-diacetate dye. A fluorescent microplate reader (BioTek Instruments, Winooski, VT, USA) was used to detect the formation of ROS. According to Thummasorn et al. (2011), Apaijai et al. (2012), and Chinda et al. (2012), the dye was stimulated at λex 485 nm and detected at λem 530 nm. By incubating cardiac mitochondria with 5-μM 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetra ethylbenzimidazolcarbocyanine iodide (JC-1) dye at 37°C for 30 minutes, the change in the cardiac mitochondrial membrane potential was ascertained. A fluorescent microplate reader was used to identify changes in the cardiac mitochondrial membrane potential. At λex 485 nm, the green fluorescence of JC-1 monomer form was stimulated and measured at 590 nm. At λex 485 nm, the JC-1 aggregate form (red) fluorescence was stimulated, and at λem 530 nm, it was identified. Heart mitochondrial membrane depolarization was thought to be indicated by a drop in the red/green fluorescence intensity ratio (Thummasorn et al., 2011; Apaijai et al., 2012; Chinda et al., 2012). After being incubated in respiration buffer, the amount of cardiac mitochondrial swelling was measured. A spectrophotometer was utilized to quantify the absorbance. Heart mitochondrial swelling was thought to be indicated by a decrease in absorbance (Thummasorn et al., 2011; Apaijai et al., 2012; Chinda et al., 2012).

Determination of cardiac mitochondrial morphology

Heart mitochondria were post-fixed in 1% cacodylate-buffer osmium tetroxide for two hours at room temperature, fixed with 2.5% glutaraldehyde in 0.1 M cacodylate buffer, and dehydrated in an ethanol graded series. After then, Epon-Aradite was embedded with cardiac mitochondria. Using a diamond knife, ultrathin slices were cut and dyed with lead citrate and uranyl acetate. Using a transmission electron microscope, the morphology of the cardiac mitochondria was studied (Thummasorn et al., 2011).

Analytical statistics

The data was shown as mean ± SE. To assess for group differences, a one-way ANOVA was utilized, followed by a post hoc Fisher's least significant difference analysis. It was deemed statistically significant when $P < 0.05$.

Outcomes

Metabolic parameters

At baseline, we observed no differences in body weight, food consumption, plasma insulin, glucose, total cholesterol, and MDA levels between ND and HFD rats Body weight, plasma insulin, HOMA index, total cholesterol, and plasma MDA levels were all significantly higher after 12 weeks of HFD consumption compared to ND rats (Table 1). In HFD rats given sitagliptin and vildagliptin, we observed significant improvements in plasma insulin, total cholesterol, HDL levels, and HOMA index. In addition, vildagliptin and sitagliptin-treated HFD rats showed improvements in both plasma and cardiac MDA levels. Nevertheless, neither medication had an impact on body weight, visceral fat weight, or plasma glucose levels. There was no discernible change between the vildagliptin-, sitagliptin-, and vehicle-treated groups.

HRV

At baseline, the LF/HF ratio did not differ between the ND and HFD groups (Figure 2A). We found that the LF/HF ratio was increased in week 8 of HFD consumption and markedly increased in week 12 (0.19 ± 0.02 at baseline, 0.26 ± 0.03 at week 8 and 0.33 ± 0.01 at week 12) (Figure 2A). After 21 days of treatment, LF/HF ratio was increased in HFD group treated with vehicle (HFDV) rats [HFDV 0.37 ± 0.02, $P < 0.05$ versus ND group treated with vehicle (NDV)]. Both vildagliptin and sitagliptin returned the LF/HF ratio to the normal level [HFD group treated with vildagliptin (HFDVil) 0.19 ± 0.01, HFD group treated with sitagliptin (HFDSi) 0.22 ± 0.03, $P < 0.05$ versus HFDV] (Figure 2B).

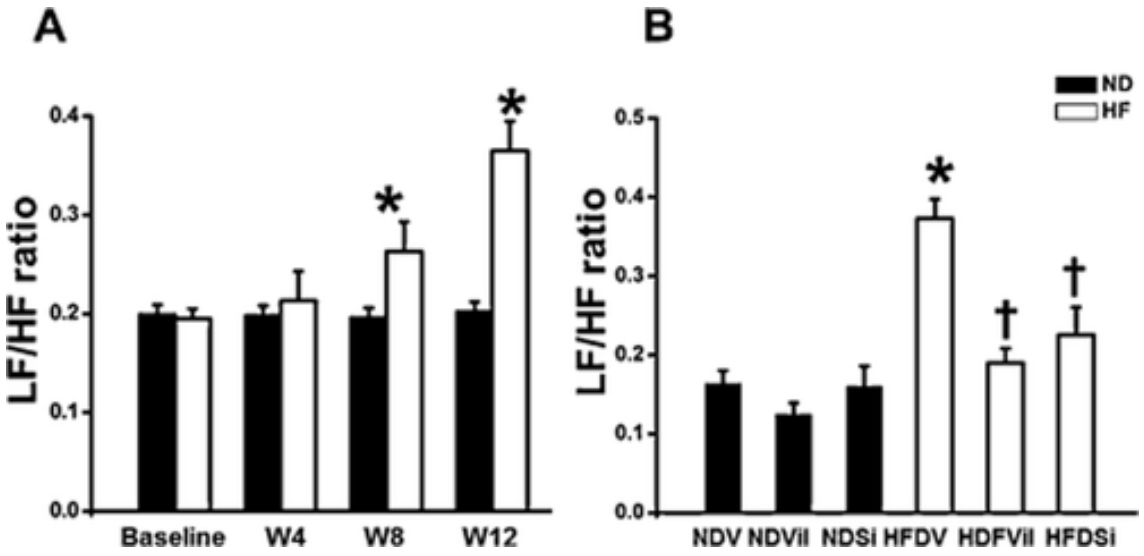

Figure 3: LF/HF ratio in ND and HFD rats (A). The LF/HF ratio significantly increased in weeks 8 and 12 of HFD consumption, in comparison with the baseline. *P < 0.05 versus baseline. LF/HF ratio in ND and HFD rats treated with vehicle, vildagliptin, and sitagliptin (B). In HFD rats, vildagliptin and sitagliptin restored the LF/HF ratio, in comparison with the vehicle. *P < 0.05 versus NDV, †P < 0.05 versus HFDV.

Cardiac function parameters

The heart function measures in the ND groups were not different between the three treatment groups . Heart failure was noted in the HFD groups receiving vehicle treatment, as evidenced by increases in HR, EDP, and −dP/dt and decreases in ESP, +dP/dt, and SV. In HFD rats treated with vildagliptin and sitagliptin, we observed significant improvements in ESP, EDP, +dP/dt, −dP/dt, and SV. When compared to the mean HR of the group treated with vehicle alone, vildagliptin treatment abolished the pathophysiologic elevation of HR, but sitagliptin treatment did not . Furthermore, we discovered that treatment groups did not differ in SBP, DBP, or SW.

Cardiac mitochondrial function and morphology

In the ND group, cardiac mitochondrial ROS production [NDV 71 ± 4 au, ND group treated with vildagliptin (NDVil) 62 ± 4 au, ND group treated with sitagliptin (NDSi) 78 ± 10 au, Figure 3], the red/green fluorescent intensity ratio, which indicated cardiac mitochondrial membrane potential change (NDV 0.35 ± 0.01, NDVil 0.35 ± 0.02, NDSi 0.35 ± 0.01, Figure 4), and the absorbance, which indicated mitochondrial swelling (NDV 0.95 ± 0.03 au, NDVil 0.94 ± 0.02 au, NDSi 0.95 ± 0.01 au, Figure 5), were not different among the three treatment groups of the ND rats. In HFD rats, an increase in cardiac mitochondrial ROS production (HFDV 164 ± 11 au, P < 0.05 versus ND group, Figure 3), cardiac mitochondrial depolarization (HFDV 0.27 ± 0.01, P < 0.05 versus ND group, Figure 4), and cardiac mitochondrial swelling (HFDV 0.83 ± 0.02 au, P < 0.05 versus ND group, Figure 5) were observed. Both vildagliptin (HFDVil 73 ± 7 au) and sitagliptin (HFDSi 86 ± 18 au) returned cardiac mitochondrial ROS production to the normal level (Figure 3). Moreover, vildagliptin and sitagliptin prevented cardiac mitochondrial depolarization (Figure 4) and cardiac mitochondrial swelling (Figure 5). In HFD rats, representative electron microscope picture illustrated unfolded cristae in cardiac mitochondrion, comparison with that in ND rats (Figure 6), indicating cardiac mitochondrial swelling. Both vildagliptin and sitagliptin prevented cardiac mitochondrial swelling in HFD rats (Figure 6).

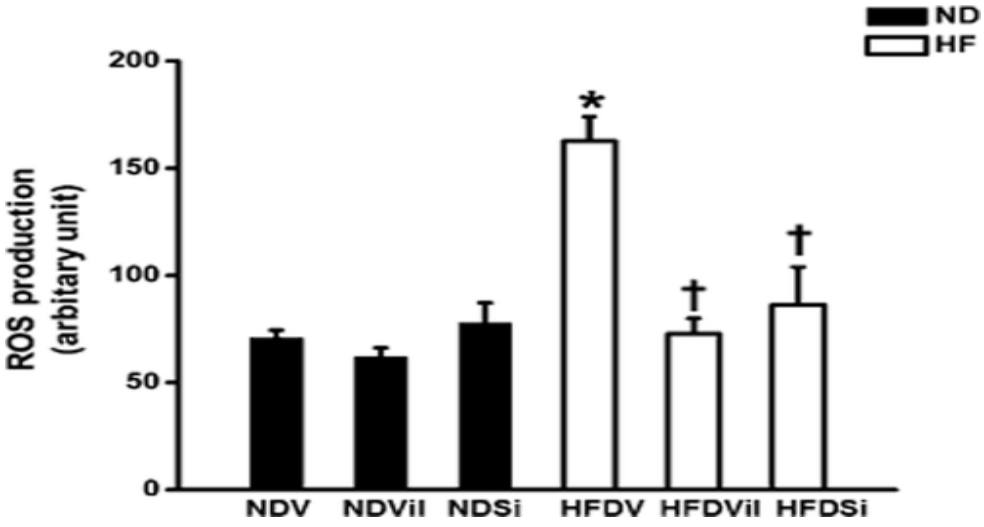

Figure 4: Cardiac mitochondrial ROS production in ND and HFD rats treated with vehicle, vildagliptin, and sitagliptin. In HFD rats, vildagliptin and sitagliptin reduced cardiac mitochondrial ROS production, in comparison with the vehicle. *P < 0.05 versus NDV, †P < 0.05 versus HFDV.

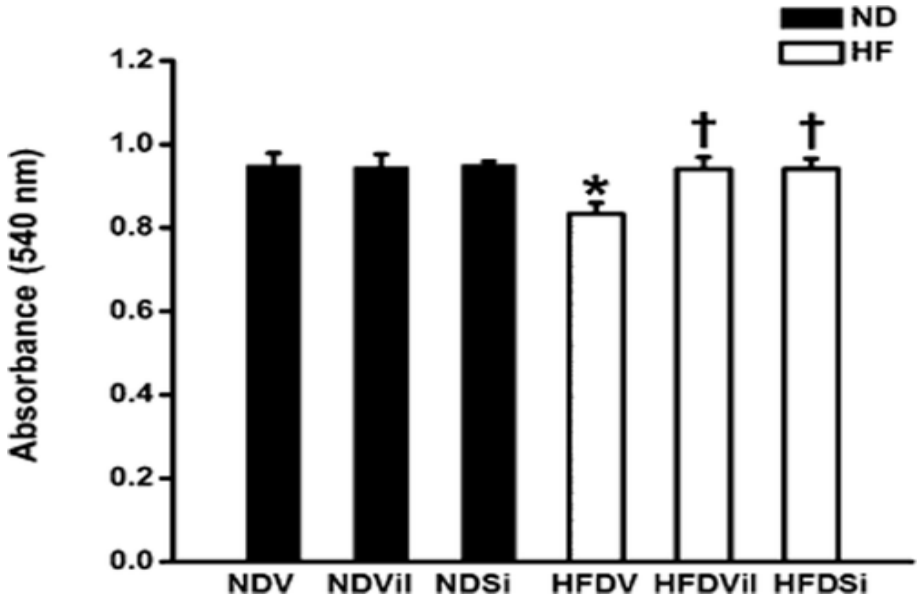

Figure 5: Cardiac mitochondrial swelling in ND and HFD rats treated with vehicle, vildagliptin and sitagliptin. In HFD rats, vildagliptin and sitagliptin reduced cardiac mitochondrial swelling, in comparison with the vehicle. *P < 0.05 versus NDV, †P < 0.05 versus HFDV.

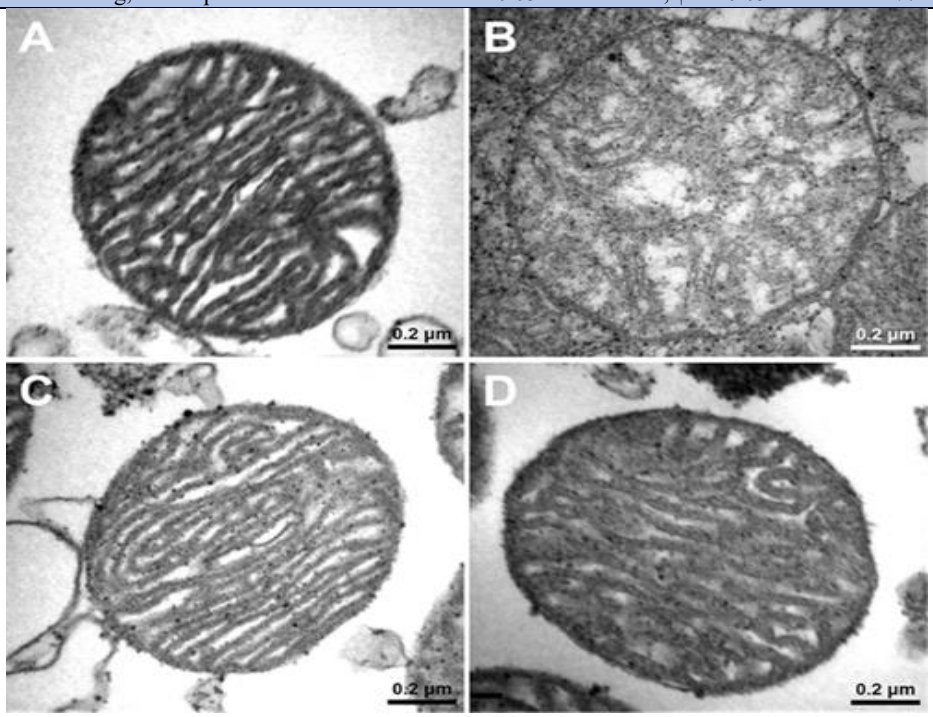

Figure 5: Electron microscope pictures of cardiac mitochondria in NDV (A) and HFD rats treated with vehicle (B), vildagliptin (C) and sitagliptin (D). In HFD rats, vildagliptin and sitagliptin prevented cardiac mitochondrial morphology changes, in comparison with the vehicle.

Discussion :

The results of this investigation demonstrate that in HFD-induced insulin-resistant rats, vildagliptin and sitagliptin enhance metabolic parameters and reduce oxidative stress. In HFD-induced insulin-resistant rats, vildagliptin and sitagliptin reduced cardiac dysfunction and preserved HRV in full. Only vildagliptin, nevertheless, was able to get HR back to normal. Furthermore, in rats with insulin resistance brought on by a high-fat diet, vildagliptin and sitagliptin retained the shape of the heart mitochondria and prevented cardiac mitochondrial dysfunction. Our model in this work involves insulin resistance brought on by a high-fat diet and is typified by hyperinsulinemia and euglycemia. Our findings demonstrated that, while plasma insulin levels in rats increased significantly at week 12 of high-fat diet consumption, plasma glucose levels in the ND and high-fat diet groups were not different at baseline or at week 12. This outcome verified that after eating a high-fat diet, these rats started to exhibit signs of insulin resistance in week 12. These results were also in line with earlier studies that used insulin-resistant rats generated by a high-fat diet (Pratchayasakul et al., 2011; Apaijai et al., 2012; Pipatpiboon et al., 2012).

Insulin resistance has been shown to be induced by long-term HFD use (Pongchaidecha et al., 2009; Pratchayasakul et al., 2011; Pipatpiboon et al., 2012). DPP-4 inhibitors, vildagliptin and sitagliptin in particular, have been demonstrated in animal and clinical research to enhance metabolic parameters and lower plasma insulin levels (Ahren et al., 2004; Mari et al., 2005; Dobrian et al., 2011; Briand et al., 2012). In the present investigation, vildagliptin and sitagliptin-treated HFD rats showed a decrease in plasma

insulin levels. Additionally, we discovered that both vildagliptin and in HFD rats, sitagliptin lowered overall plasma cholesterol levels. This result is in line with earlier research showing that sitagliptin and vildagliptin reduced plasma cholesterol levels in type 2 diabetic patients (Kleppinger and Helms, 2007; Tremblay et al., 2011), HFD mice (Flock et al., 2007), and normal rats (Yin et al., 2011). Additionally, our study is the first to demonstrate that, in long-term HFD-induced insulin-resistant rats, sitagliptin and vildagliptin could raise plasma HDL levels while having no effect on plasma glucose or LDL/VLDL levels. Vildagliptin and sitagliptin have been shown in prior clinical investigations and in rats with both type 2 diabetes and normal blood pressure to lower oxidative stress levels (Read et al., 2010; Matsui et al., 2011; Chinda et al., 2012; Goncalves et al., 2012). In In this investigation, we discovered that vildagliptin and sitagliptin-treated HFD rats had lower plasma and cardiac MDA levels. These results suggest that in obese insulin-resistant rats fed a long-term high-fat diet, both sitagliptin and vildagliptin may lessen the state of insulin resistance and oxidative stress.

A frequently used metric linked to autonomic regulation function, heart rate variability (HRV) is an indicator used to assess cardiac sympathovagal balance (Chattipakorn et al., 2007; Incharoen et al., 2007; Kumfu et al., 2012). Our research showed that the LF/HF ratio rose in HFD-consuming rats throughout weeks 8 and 12, with a notable rise occurring during week 12. This suggests a cardiac sympathovagal imbalance. This study demonstrated that by bringing the LF/HF ratio back to normal, sitagliptin and vildagliptin both restore the HRV. Due to a rise in In this investigation, we discovered that vildagliptin and sitagliptin-treated HFD rats had lower plasma and cardiac MDA levels. These results suggest that in obese insulin-resistant rats fed a long-term high-fat diet, both sitagliptin and vildagliptin may lessen the state of insulin resistance and oxidative stress.

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Our research and other research have demonstrated that different diets can cause cardiac dysfunction in obese insulin-resistant rats (McCann et al., 1995; Sun et al., 2011; Apaijai et al., 2012). In line with earlier findings, this study indicated that long-term HFD consumption leads to heart impairment. Insulin-resistant HFD-induced rats showed a considerable improvement in cardiac function after receiving treatment with vildagliptin and sitagliptin. Their ability to prevent cardiac mitochondrial dysfunction may be the cause of their cardioprotective benefits.

Heart mitochondria are in charge of providing the right amount of energy to keep the heart functioning normally. According to earlier research (Kraegen et al., 2008; Coletta and Mandarino, 2011), insulin resistance is linked to mitochondrial dysfunction in a number of insulin target tissues, including the heart. According to Thummasorn et al. (2011) and Chinda et al. (2012), we discovered that cardiac mitochondrial dysfunction occurred in HFD rats, as evidenced by increased cardiac mitochondrial ROS generation, depolarization of the mitochondrial membrane, and swelling of the cardiac mitochondria. Vildagliptin has been shown by Chinda et al. to reduce the formation of reactive oxygen species (ROS) and depolarization of the mitochondria in the heart in oxidatively stressed isolated cardiac mitochondria (Chinda et al., 2012). Furthermore, Thummasorn et al. noted that cardiac mitochondrial ultrastructure may be harmed by extreme oxidative stress (Thummasorn et al., 2011). In this study, we observed that in obese insulin-resistant rats fed a long-term high-fat diet, cardiac mitochondrial dysfunction was avoided by both sitagliptin and vildagliptin Our research revealed that the obese insulin-resistant rats exhibited cardiac autonomic dysfunction, indicated by a decreased heart rate variability (HRV), cardiac mechanical dysfunction, indicated by abnormal cardiac pressure-volume data, and cardiac mitochondrial dysfunction, indicated by an increase in the production of reactive oxygen species (ROS), depolarization of the mitochondrial membrane, and swelling of the mitochondria. In this investigation, we discovered that sitagliptin and vildagliptin both offered cardio protection through their advantages in preventing cardiac mitochondrial dysfunction, which included a reduction in ROS production. halted mitochondrial swelling and restored the potential of the mitochondrial membrane. Since it is well known that increased ROS production primarily contributes to mitochondrial depolarization and swelling, the main reason why both medications attenuated the depolarization of the mitochondrial membrane in these obese insulin-resistant rats may have been because they reduced the production of ROS within the mitochondria. The medications' capacity to lower plasma MDA was another indication of their anti-oxidative action. These results suggested that these DPP-4 inhibitors' cardioprotective benefits in these obese insulin-resistant rats may be mostly due to their anti-oxidative properties.

Conclusion :

Ultimately, long-term HFD-fed rats showed signs of insulin resistance, elevated oxidative stress, cardiac sympathovagal imbalance, cardiac dysfunction, and cardiac mitochondrial dysfunction. When long-term HFD consumption produced insulin-resistant animals, vildagliptin and sitagliptin both reduced oxidative stress and cardiac mitochondrial dysfunction and improved insulin-resistant condition, HRV, and cardiac function.

Conflict of interest

None

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