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Ameliorative effect of apelin on streptozotocin-induced diabetes and its associated cardiac hypertrophy

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ABSTRACT

Aim: Apelin, an adipocyte-derived factor, exhibited a number of cardioprotective properties; however, its effect in diabetes which is a major risk factor for cardiovascular disease (CVD) needs to be further studied. So this work was designed to evaluate the effect of apelin on diabetes and its associated cardiac hypertrophy with its possible underlying protective mechanisms.

Experimental protocol: Thirty male adult Wistar rats were categorized into three groups, 10 rats each, normal control group: received standard food and water regime. Diabetic control group: received streptozotocin (STZ) at a dose of (55 mg/kg, i.p., once) dissolved in citrate buffer (pH 4.5). Apelin-13 treated diabetic group: STZ diabetic rats received an intra peritoneal injection of apelin-13 at a dose of (100 nmol/kg/day), and given daily for 8 weeks. at the end of the experiment, oral glucose tolerance test (OGTT) was assayed, then rats were sacrificed and serum glucose, insulin, triglyceride (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, serum lactate dehydrogenase (LDH) and serum creatine kinase – MB (CK-MB) were measured, together with cardiac hypertrophy index (CHI), left ventricular hypertrophy index (LVHI) and left ventricular protein and collagen content levels. Myocardial superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and malondialdehyde (MDA) were determined in the myocardial tissue of experimental rats.

Results: Treatment with apelin-13 improved hyperglycemia and hyperlipidemia, and significantly protected against STZ-induced structural alterations in cardiac tissue, it also produced a significant reduction in MDA while it elevated the level of antioxidant enzymes in hearts of diabetic rats.

Conclusion: This study suggested that apelin can ameliorate diabetes and its associated myocardial hypertrophy through mainly its anti diabetic, anti hyperlipidemic and anti oxidative stress properities.

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1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases caused by a complex interaction of genetic, immunological and environmental factors. DM is very common and it is a prime risk factor for CVD, including diabetic cardiomyopathy.[1]

Diabetic cardiomyopathy has been defined as a ventricular dysfunction that occurs in diabetic patients independent of a recognized cause, such as coronary artery disease or hypertension.[2] The hallmark characteristic of diabetic cardiomyopathy is a subclinical phase associated with cellular structural abnormalities including cardiomyocyte hypertrophy, cardiac inflammation, fibrosis and increased apoptosis which lead initially to diastolic dysfunction, later to systolic dysfunction and eventually to heart failure.[3]

The pathophysiology of the link between diabetes and CVD is complex and multifactorial, though unclear.[4] However, the occurrence of hyperglycemia, hyperlipidemia, and oxidative stress in diabetes has been extensively documented, and is implicated in the pathogenesis of various cardiovascular complications including cardiomyopathy.[5] Thus, among the various therapeutic strategies, antihyperglycemic, antihyperlipidemic, and antioxidant agents can be useful in the prevention of cardiomyopathy in STZ induced diabetes.[6]

Apelin, a small regulatory peptide, had been identified as the endogenous ligand of the human orphan G protein coupled receptor (GPCR) which is a receptor structurally related to the angiotensin II (ANG II) receptor AT1 but does not bind to angiotensin II, thus it was previously designated as an "orphan" GPCR, having no known ligand, and was named APJ.[7] Later, it was identified that apelin is the endogenous ligand for this receptor, thus The

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approved Human Genome Organization (HUGO) gene symbol for APJ is now apelin receptor (APLNR).[8]

Apelin is synthesized as a 77 amino acid pre-pro-peptide that can be cleaved into fragments of different sizes that activate APLNR, with apelin-13 is the final active product, being the most potent isoform and more resistant to enzymatic cleavage.[9] Apelin is secreted mainly from white adipose tissue, however it can also be expressed in different tissues as kidney, heart, lung and many areas in the brain.[10]

Apelin peptides have been shown to affect many biological functions in mammals including neuroendocrine, cardiovascular, and immune systems and it can act via autocrine, paracrine, endocrine, and exocrine signaling.[11]

In recent years, apelin have been studied for its anti-obesity and anti diabetic properties and it was recorded that apelin-13 may have beneficial effects in metabolic disorders and its associated complications.[7]

Acute intravenous injection of apelin had been shown to produce a powerful glucose-lowering effect associated with improved glucose tolerance in high fat fed mice which were glucose intolerant or frankly diabetic,[12] also chronic treatment with apelin in obesity-induced type II diabetic model improved hyperglycemia, and insulin sensitivity but it was associated with elevated levels of TG.[10] Furthermore, it was recorded that there was a negative correlation between apelin blood levels and glycosylated hemoglobin (HbA1c) levels in diabetic patients, this indicated that higher apelin levels were associated with lower HbA1c levels and better glucose control, but this was only significant for type II diabetic patient.[13]

In type I diabetes, the effect of apelin is markedly questionable. Early studies recorded that the increased circulating level of apelin in children with type I DM had no significant relation with glucose, lipids, adiponectin levels, and insulin sensitivity,[14] however, it had been shown recently that apelin had a hypoglycemic effect and could improve pancreatic beta cell function and lower the serum triglycerides in type I diabetic model.[10] Thus apelin's role in glucose and lipid homeostasis in type I diabetes needed further investigations.

Furthermore, It had been shown that dysregulation of the apelin/APLNR system may be involved in the predisposition of cardiovascular diseases, and enhancing apelin action may have important therapeutic effects, especially that some studies recorded decreased serum level of apelin in cardiovascular diseases.[15] also, apelin proved its cardioprotective effect in different animal models, as in cardiac ischemia reperfusion injury,[16,17] isoproterenol-induced cardiotoxicity[18] and heart failure models,[19] however its effect in diabetic cardiomyopathy is still needed to be further highlighted.

Thus, I extended this current study to investigate the anti diabetic and cardioprotective effects of apelin in STZ induced diabetic rat model, delineating its different mechanisms of action in ameliorating the course of this disease progression.

2. Material and methods

2.1. Animals and experimental design

This study was carried out on thirty male adult Wistar rats weighing about 200–250 g. The rats were housed, four per cage, under standard laboratory conditions at room temperature (24 ± 2 °C), and had free access to water and food. The rats were fasted during the night before the experiment. All animal experiments were undertaken with the approval of Ethical Animal Research Committee of Tanta University.

The rats were randomly divided into three groups (10 rats each).

2.2. Normal control group

Rats were maintained on standard food and water regime.

2.3. Diabetic control group

An experimental model of diabetes was induced by intra peritoneal injection of STZ (55 mg/kg body weight) (Sigma–Aldrich Chemical, Steinheim, Germany) dissolved in Na citrate solution adjusted at pH 4.5, The control animals were injected with equal volume of vehicle.[20]

STZ is anti microbial agent with a selective cytotoxicity to pancreatic β-cells that has the ability to induce a specific necrosis and destruction of the pancreatic β-cells and thus it is the first choice for diabetes induction in animals.[21] This cytotoxicity to β-cells is mediated through DNA break, nitric oxide production and Free radical generation.[22]

Because of streptozotocin's ability to induce fatal hypoglycemia as a result of massive pancreatic insulin release, the rats were provided with 10% glucose solution after 6 h of STZ administration for the next 48 h to prevent hypoglycemia. Rats with diabetes (blood glucose >200 mg/dl) were selected for this experiment.[23]

2.4. Apelin-13 treated diabetic group

Intraperitoneal injection of apelin-13 (Apelin, Phoenix Pharmaceutical, Belmont, CA, USA), was given at a dose of (100 nmol/kg/-day) dissolved in saline and treatment was started after 3 days of STZ injection, furthermore control diabetic group was injected daily with saline via the intraperitoneal (IP) route.[24]

Weekly body weight gain was measured and at the end of the experiment (8 weeks) from induction of diabetes, the following parameters were determined.

2.5. Oral glucose tolerance test

The animals were subjected to oral glucose tolerance test (OGTT).[25] To perform OGTT, the animals were fasted at least 5 h after the last meal, then they were orally administered with 1.5 g/kg glucose and blood samples were collected from the tail vein under light ether anesthesia before, and at intervals of 0 min and 30, 60 and 120 min after oral glucose administration. Samples were analyzed for glucose and insulin as mentioned above. Plotting the glucose concentration versus time gives a curve showing rise and fall in glucose and insulin levels with time and results are expressed as integrated area under the curve (AUC) for glucose and insulin.

AUC glucose and insulin levels were calculated using the trapezoidal method which depends on an interpolation between data points of glucose and insulin levels measured during OGTT. For a given time interval (t1–t2), the AUC can be calculated as follows:

$$AUC = (C1 + C2)/2 \times (t2 - t1)[26]$$

In essence, the first two terms (C1 + C2) calculate the average concentration over the time interval, while the last piece (t1–t2) is the duration of time. So this method takes the average concentration of glucose and insulin and applies it to the entire time interval, sum of all the intervals together, gives the total AUC.[27]

2.6. Blood sampling and biochemical analysis

The rats were sacrificed by cervical decapitation and overnight fasting blood samples (8 ml/rat) were taken, and allowed to clot for 2 h at room temperature before centrifugation for 20 min at approximately 5000 rpm[28] was done. The separated serum was stored at −20 °C till the time of measurement. Repeated freezing and thawing were avoided.

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