The Effect of 12 Weeks Aerobic Training on the Mafa Gene Expression of Pancreas in the Male Wistar Rats Type 2 Diabetes

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Abstract

Objective: MafA is one of the major factors in the family of MafA transcription factors. In pancreatic beta cells, MafA plays an important role in regulating the expression of glucose-dependent Insulin gene. On the other hand, Lipotocyticleads to negative expression of MafA expression when exposed to inflammatory cytokines. These statements in general emphasize the role that MafA plays as a key regulator of genes that are effective in maintaining the function of beta cells and glucose-dependent insulin synthesis.

Materials and Methods: Considering the very important role of MafA transcription factor in the protection and function of beta cells and insulin secretion, In order to investigate the effect of exercise activities on expression of this gene, 16 male Wistar rats were divided into diabetic control and diabetic training groups. The two groups were diabetic with receiving nicotinamide and streptozotocin injection and the experimental group was trained for 12 weeks by aerobic exercise on a treadmill.

Results: The results of the study showed a significant increase in the expression of the MafA gene after 12 weeks of aerobic training, which resulted in a significant decrease in blood glucose concentration and increased beta cell function.

Conclusion: Based on the evidence of the mechanisms responsible for the synthesis and secretion of insulin in the pancreatic beta cells, it can be concluded that increased levels of insulin levels in aerobic intervention group rats in the present study it is rooted in increasing the expression of MafA compared to the control group.

Keywords: Gene expression, Pancreatic beta Cells, Diabetes mellitus type 2, Aerobic exercise

Introduction

Type II diabetes is considered as the most common intravenous disease caused by glucose intolerance due to the balance between reserves and insulin demand and is one of the main causes of mortality and many chronic diseases (1,2). Among the factors that affect type 2 diabetes such as weight, age, gender, genetics, physical activity and ..., obesity is most important (3). Under these conditions, the response of insulin receptors in target tissues is disrupted that is accompanied with the phenomenon of insulin

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resistance or decreased insulin sensitivity in the target tissue (4). Recent evidence strongly supports the assumption that the main problem with the spread or progression of type 2 diabetes mellitus is not limited to insulin receptors in target tissues. Both environmental and genetic factors affect the incidence and severity of type 2 diabetes. One of the most effective genetic mechanisms in this disease is abnormal beta cell function, as genetic factors affect insulin secretion from beta cells in both types of diabetes (5,6). In addition to the presence of insulin resistance, the prevalence or progression of type 2 diabetes also appears to be rooted in other molecular cellular disorders, such as genetic disorders (7). As in the past decade, the potential role of transcription factors in the secretion of insulin from beta cells has been raised in diabetic or pre-diabetic individuals (8). In the meantime, genetic factors, in other words, numerous transcription factors that affect the mass or number of beta cells and some kind of insulin synthesis, are listed by laboratory studies that include TCF7L2, PDX-1, GLP-1, MTNR1B, GLUT2, MafA, NeruD1 and FoxO1 that is one of the most important. Disruption of the gene expression of each of them either alone or in collaboration with other genetic factors affects the process of insulin biosynthesis in the pancreatic tissue (9). MafA is an insulin-like gene transcription factor that is expressed in the onset of the secondary transfer process in beta cells (10,11). Similar to NeuroD, MafA levels also increase in response to H2O2 under oxidative stress conditions of beta cells. In terms of oxidative stress, FoxO1 binds to the MafA promoter. Probably MafA is one of the target genes of FoxO1 in beta cells of the pancreas (12). MafA regulates the transcription of insulin and other glucose-sensitive genes in pancreatic beta cells (13-15). Increasing glucose concentration increases temporarily the ability of MafA to bind and function through (RIPE3b1 / X1 DNA element), which is known to be a key factor in the regulatory sequence of the promoter of genes that are effective in secretion of insulin (16-18). Recent studies have revealed that the creation of stress conditions in beta cells, resulting in decreased expression of some transcription factors such as PDX1, Mafa, and NKX6.1 in type 2 diabetic rats and humans, may lead to decreased growth and function of beta cells (19-21). In humans, the expression of Mafa is strongly reduced in beta cells in type 2 diabetic patients. This phenomenon has also been revealed in mice with type 2 diabetes. In addition, increased expression of Mafa is associated with a reduction in oxidative stress in beta cells and an increase in the expression of insulin, GLUT2 and Slc2a2 (22). The dysfunction of beta cells in type 2 diabetes status in related to stressed is probably due to the gradual reduction of Mafa, which results in decreased expression of PDX1 and NKX6.1 in pancreatic cells, such that Mafa-free mice have glucose intolerance and Reducing the expression of PDX1 and NKX6.1 will immediately lead to severe hyperglycemia (23-26). It is known that increasing the expression of Mafa in conditions of oxidative stress associated with obesity and dyslipidemia in obese mice leads to an improvement in blood glucose levels. However, studies have shown that increasing insulin secretion and beta cells to glucose due to increased expression of Mafa in cells is also dependent on the variability of some other genetic factors, such as Slc2a2, and glucose transporters in beta cells such as GLUT2 (27). However, less studies have been conducted to investigate the response of these genetic factors, especially FoxOl and MafA, to the various exercise interventions and the effect of their alteration through exercise interventions on insulin and glucose levels in diabetic populations. Therefore, due to limited studies as well as some contradictory findings in other genetic factors, the present study was conducted to determine the effect of 3 months aerobic exercise on the expression of MafA in pancreatic tissue of type 2 diabetic rats.

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Materials and Methods

The statistical population was selected from all male rats of the animal's house of the Institute of Pasteur which of them16 male Wistar rats (at the age of ten weeks and weighing 220 ± 20 gr) were randomly selected to participate in the study. Subsequently, Wistar rats, all of which have similar physical and age characteristics, were randomly assigned to two groups including the diabetic control group and the aerobic diabetic group. Rats in Animals' Laboratory of Parand Islamic Azad University in a 5-by-10-meter-wide room under controlled light conditions (12 hours of light and 12 hours of darkness, 6-evening lighting start and 6-morning darkness start) with temperature (22 ± 3°C) and moisture maintained at a range of 30 to 60. At first, the rats became acquainted with the environment for 2 weeks with the living conditions of the animal house and how to run on the treadmill. Then, after a fasting night (12 hours), nicotineamide and streptozotocin were used to induce type 2 diabetes. Initially, a solution of nicotinamide at a dose of 110 mg per kg of rat mice was injected peritoneally; after 15 minutes, the freshly prepared STZ solution in the citrate buffer with PH = 4.5 was also injected intraperitoneally at a dose of 60 mg Grams per kilogram. One week after diabetes induction, fasting blood glucose and glucose levels above 150 mg / dL were considered as a measure to ensure that mice were diagnosed with type 2 diabetes (28). A training program for 12 weeks aerobic exercise of 5 sessions per week with gradual increase in speed (18-26 m / min) and time (10 to 55 minutes) in the form of running on treadmill with the aim of determining its effect on the function of beta cells and expression The relative proportions of Mafa in the pancreatic tissue were compared to the control group that did not participate in the training program.48 hours after the last training session (10-12 hours fasting), The rats in each group were anesthetized by intraperitoneal injection of ketamine 10%, at a dose of 50 mg / kg blended with zylosin 2% at a dose of 10 mg / kg. After assuring anesthesia, the animal's chest was taken by a split surgical blade and blood samples were taken directly from the animal's heart. Blood samples were centrifuged at 1000 × gr for 20 minutes to isolate the serum and stored at 80 ° C for glucose and insulin measurement. Then the chest of the animal was split and the pancreatic tissue of the rats was sampled and after washing in a physiologic serum in a 1.8 microtiter containing RNAlaterTM liquid, immersed in a ratio of 20% and transferred to the laboratory for genetic testing. Also, beta cell function was calculated from the insertion of fasting insulin and glucose in the software (HOMA2-Calculator). All statistical analyzes were performed using SPSS software version 16. The Kolmogorov Smirnov test was used to ensure the normal distribution of data. Data analysis was performed using independent t-test. Changes were less than 5% significant.

Results

Table 1 shows the pattern of body weight changes pre and post aerobic training in the aerobic diabetic group and the diabetic control group. (Based on the results of dependent T-test).

- In diabetic control group, rats' weight increased significantly compared to pre-test (P <0.001).
- In the aerobic diabetic group, rats' weight increased significantly compared to the pre-test (P <0.001).

According to Table 2, Aerobic training significantly increased the relative expression of MafA in the pancreatic tissue of the aerobic diabetic group compared to the diabetic control group.

According to Table 3, aerobic training caused a significant reduction in fasting glucose in the aerobic diabetic group compared to the diabetic control group.

Table 4 shows that, aerobic training significantly increased serum insulin in aerobic diabetic group compared to diabetic control group.

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Table 1. Body weight changes (g) in pre and post training conditions (Standard deviation + average)

Group	Before training	After training	Sig
Diabetic control	220 ± 3.34	254 ±5.96	<0.001
Aerobic diabetic	225 ± 2.61	241 ±2.24	<0.001

Table 2. Relative expression of MafA in Aerobic and Controlled Diabetic Groups

Variable	Diabetic control group	Aerobic diabetic group	Sig
Relative expression of MafA	1	1.45±1.21	0.044*

Table 3. Fasting glucose levels in aerobic and control Diabetic groups

Variable	Diabetic control group	Aerobic diabetic group	Sig
Glucose (mg / dL)	294±11	240±14	0.000*

Table 4. Serum insulin levels in aerobic and control groups

Variable	Diabetic control group	Aerobic diabetic group	Sig
Insulin (µIU / ml)	4.06±0.21	5.11±0.25	0.000*

Discussion

A review of research evidence suggests that the findings of some studies on the response to diabetes determinants to exercise training are not consistent. so that In some studies, weight loss and body fat levels were reported along with the improvement of diabetes-induced indices (29). On the other hand, in some studies, there has been a significant improvement in the components of diabetes determination in the absence of changes in weight and other metabolic components (30,31). Some studies also reported improvements in blood glucose or insulin levels and other components such as beta cell function in changing or no changing of inflammatory mediators (31-33). The contradiction in the findings suggests in some way that changes in the determinants of diabetes in response to exercise or other internal or external stimuli are rooted in other factors. In this context, the genetic factor should not be ignored. Because recent studies have strongly supported the role of genetic and inheritance in the prevalence or severity of diabetes (22,23). In the present study, the effect of 12 weeks aerobic training on the expression of Mafa gene in pancreatic tissue of type 2 diabetic rats was measured as compared to the control group that did not participate in the training program. Based on the available evidence, it is hypothesized that a change in the expression of this transcription factor in response to Continuous exercise training will improve the components of diabetes determination such as glucose levels and synthesis or serum insulin levels. so that Long-term exposure to hyperglycemic laboratory mice results in decreased expression or activity of Mafa and other transcription factors such as PDX-1, which in turn leads to dysfunction of beta cells (34). The transcription factors of MafA, NeourD1, and PDX-1 in a consistent pattern in response to increased glucose entry to beta cells by GLUT2 stimulate the expression of insulin gene expression (35,36). On the other hand, both Mafa and NeourD1 are the target genes of FOXO1 in pancreatic cells (12). Laboratory studies have revealed that the expression of Mafa decreases in the presence of type 2 diabetes (12). On the other hand, its reduction is associated with a decrease in the synthesis and secretion of insulin from beta cells of the pancreas (10,11). In one study, 6 weeks of optional running could reduce the genesis of impaired gene expression in beta cells such as MafA, to a non-significant extent (37). Also In this study, fatty diets aimed at inducing type 2 diabetes resulted in decreased expression of certain target genes in pancreatic beta cells, such as GLP-1, GIP-R, MafA and also PDX-1 receptors, which reduced the synthesis and secretion of insulin Leading to pancreatic cells. But performing exercise exercises in the form of optional running for 6 weeks, except for a significant increase in insulin expression, was not associated with a significant change in other transcription factors (37). However, in

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another study, an 8-week aerobic training led to an increase in the expression of PDX-1 and beta-cell function in dawley Sprague female rats (38). In another study, the use of 8 weeks of aerobic training led to an increase in the expression of MafA in beta cells of the pancreas in rats fed with high-fat diets (4). In this regard, the findings of the present study suggest an increase in the expression of Mafa following 12 weeks of aerobic training in type 2 diabetic rats. In other words, 12 weeks of aerobic training led to an increase in the relative expression of Mafa in the pancreatic tissue, with an increase in serum levels of insulin and a decrease in fasting glucose. It should be noted that in the pancreas, Mafa is expressed exclusively in beta cells (10,14). Hence, the increase in serum insulin can be attributed to the increased expression of Mafa in response to training intervention. In pancreatic beta cells, MafA plays the role of regulating the expression of insulin -dependent glucose gene. It also plays a role in controlling and regulating some proteins and other genes such as PDX-1 (39-41). The levels of MafA in pancreatic cells are regulated by post-translational mechanisms such as serine phosphorylation of 14 and 65. High levels of expression of MafA in beta cells have a central role in regulating other genes that are effective in maintaining the function of beta cells in response to glucose (42). MafA-free mice can continue to live, but MafA's inactivity leads to the continuation and increased severity of diabetes as a result of lowering insulin secretion from beta cells in the pancreas (42-44). Increasing MafA production at high concentrations of glucose can regulate insulin -dependent glucose gene transcription. While decreasing production or decreasing its expression is likely to rapidly lead to inhibiting insulin transcription. These results point to the fact that the process of transcription of insulin requires positive regulation or enhancement of the expression of MafA in beta cells (43). On the other hand, lipotocytes or exposure to inflammatory cayokins leads to negative regulation of MafA expression (42,45,46). These statements in general emphasize the role that MafA plays as a key regulator of genes that are effective in maintaining the function of beta cells andSynthesis of glucose-dependent insulin. The regulation of activity and expression of it as a key therapeutic goal in beta cell dysfunction are in response to injury (42). Increasing oxidative stress in the pancreas leads to a reduction in the binding of MafA to the insulin gene, which in turn leads to insulin gene deficiency and its synthesis and secretion from the pancreatic beta cells (47,48). It has been shown that this protein is expressed when the glucose concentration in the pancreatic beta cells reaches 0.8 mm, as well as when prolonged exposed in the presence of high levels of glucose (11.1 mmol) (48). Apart from this, the levels of MafA protein are able to increase the expression of the insulin gene in the long-term presence of high levels of glucose (47,48).

Conclusions

Based on the evidence of the mechanisms responsible for the synthesis and secretion of insulin in the pancreatic beta cells and the findings of the present study, it can be concluded that increased levels of insulin levels in aerobic intervention group rats in the present study it is rooted in increasing the expression of MafA compared to the control group. In other words, a long-term aerobic intervention of 5 sessions per week has led to an increase in the expression of MafA to increase the synthesis and secretion of insulin from beta cells in the pancreas. In this regard, although a study that seeks to directly influence the aerobic exercise on the expression of MafA in the pancreatic tissue of diabetic rats, is not seen.

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