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Research Article

Effects of Mad Honey on Blood Glucose and Lipid Levels in Rats With Streptozocin-Induced Diabetes

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Abstract: This study investigated whether mad honey affects blood glucose and lipid levels in experimental animals. It was found that mad honey caused significant decreases in blood glucose and lipid levels in animals with streptozocin-induced diabetes mellitus (n = 10) and controls (n = 10). These decreases may be due to grayanotoxins in the mad honey causing the islets of Langerhans in the pancreas to secrete insulin by stimulating the parasympathetic nervous system or M_2-muscarinic receptors.

Key Words: Blood glucose, blood lipids, mad honey, streptozocin-induced diabetes.

Streptozosin İndüklü Diabetli Ratlarda Deli Balın Kan Glukoz ve Lipid Seviyeleri Üzerine Etkisi

Özet: Bu çalışmada, deney hayvanlarında deli balın kan glukoz ve lipid seviyeleri üzerine etkisi olup olmadığını araştırmak amaçlanmıştır. Deli balın hem streptozosin indüklü diabetes mellituslu (n = 10) hem de kontrol (n = 10) hayvanlarında kan glukoz ve lipid seviyelerinde anlamlı bir düşmeye sebep olduğu bulundu. Kan glukoz ve lipid seviyelerindeki bu düşüş, deli balda bulunan grayanotoksinlerin parasempatetik sinir sistemini veya M_2-muskarinik reseptörleri uyararak pankreas Langerhans adacık hücrelerinden insülin salgılatmasına bağlı olabilir.

Anahtar Sözcükler: Kan glukozu, kan lipitleri, deli bal, streptozosin-indüklü diabet

Introduction

Rhododendron ponticum, a member of the botanical family Ericaceae, grows extensively on the mountains of the eastern Black Sea area of Turkey (1,2). Its flowers are pink or violet. All parts of this particular species, including the nectar, contain toxic diterpenes known as grayanotoxins. Ingestion of honey derived from this plant may cause profound hypotension and bradycardia (3,4). This honey is known locally as "mad honey".

In 1983, Gossinger et al. (5) reported a patient with honey intoxication who consumed honey brought from Turkey. Biberoglu et al. (6) reported 16 honey intoxication cases from Trabzon, Turkey. The latest report, by Onat et al. (7), described 2 honey intoxication cases from Trabzon, Turkey. They reported that grayanotoxin-contaminated honey extract was not bradycardic in bilaterally vagotomized animals. They suggested that the sites of cardiac and respiratory actions are within the central nervous system, and that the bradycardic effect of grayanotoxin is mediated by vagal stimulation at the periphery (7). In another study, the same researchers reported that atropin sulfate improved both bradycardia and respiratory rate depression. AF-DX 116, which is a selective M_2-muscarinic receptor

antagonist, restored heart rate, but not the respiratory rate depression, and they claimed that M_2-muscarinic receptors are involved in the cardiotoxicity of grayanotoxins (8).

Mad honey is used traditionally in the management of diabetes mellitus in east Anatolia, Turkey. People believe that it decreases the blood glucose, and so they recommend the use of this honey for diabetic subjects. This study investigated whether mad honey affects on blood glucose and lipid levels in experimental diabetic animals.

Materials and Methods

Ten male albino Wistar rats weighing 180-230 g, as the experimental group, and 10 male albino Wistar rats weighing 180-230 g, as the control group, were used. The rats were fed standard laboratory chow and water before the experiment. They were fasted overnight. The fasting blood glucose and lipid (cholesterol, triglyceride and very low density lipoprotein (VLDL)) levels were measured at 9.00 a.m. in both groups. Streptozocin (60 mg/kg dose), an experimental diabetogenic substance, was dissolved in pH 4.5 citrate buffer and administered intraperitoneally to the animals in the experimental group. The fasting blood glucose levels were measured again after 2 days in this group. Streptozocin administration resulted in high levels (239.2 ± 41.97 mg/dl) of blood glucose after 2 days. All animals in the experimental group were evaluated as experimental streptozocin-induced diabetes mellitus. On the first day (3rd day of streptozocin administration), 2 ml of mad honey (at a dose of 50 mg/kg) dissolved in distilled water was administered by oral gavage to all animals in both groups. One hour later the blood glucose was measured. Before and after the administration of mad honey blood glucose levels were measured from tail vein using glucose oxidase sticks for 3 days, always at 9.00 a.m. On the third day, the lipid (cholesterol, triglyceride and VLDL) levels were measured by spectrophotometry from tail vein blood.

The results are expressed as means and standard deviations. One sample analysis in the SPSS 10.0 for Windows program was used to evaluate the significance of differences in paired data (9).

Results

The fasting blood glucose level was 47.8 ± 5.93 mg/dl in the experimental group and 49.5 ± 6.54 mg/dl in the control group. The difference between the 2 groups in terms of fasting glucose levels was not significant ($t = 0.63$, $P = 0.54$).

Table 1 shows the levels of blood glucose before and after the administration of mad honey for the first 3 days in the control group. The treatment with mad honey caused a significant decrease in the blood glucose levels for the first, second and third days and the mean of 3 days (respectively $t = 3.59$, $P = 0.006$; $t = 2.95$, $P = 0.02$; $t = 2.86$, $P = 0.02$; $t = 4.15$, $P = 0.002$).

The blood cholesterol, triglyceride and VLDL levels were 50 ± 3.77, 48.8 ± 17.82 and 19.6 ± 3.81 mg/dl before the administration of mad honey in the control group. The blood cholesterol, triglyceride and VLDL levels were 43 ± 3.13, 27.2 ± 4.18 and 13.4 ± 1.58 mg/dl after the mad honey treatment in the control group (Table 2). The differences between before and after the administration of mad honey were statistically significant (for cholesterol, $t = 4.18$, $P = 0.002$; for triglyceride, $t = 4.18$, $P = 0.002$; for VLDL, $t = 4.03$, $P = 0.003$).

Table 1. The levels (mg/dl) of blood glucose before and after the administration of mad honey for the first 3 days and the mean of 3 days in the control group (N = 10).

	Before treatment		After treatment	
Parameters	Mean	SD	Mean	SD
Blood glucose (the first day)	71.8	9.03	63.6	10.91
Blood glucose (the second day)	91.4	27.38	79.4	29.89
Blood glucose (the third day)	94.8	29.94	73.8	13.1
Blood glucose (the mean of 3 days)	86	13.75	72.27	13.21

Table 2. The levels (mg/dl) of blood cholesterol, triglyceride and VLDL before and 3 days after the administration of mad honey in the control group (N = 10).

	Before treatment		After treatment	
Parameters	Mean	SD	Mean	SD
Blood cholesterol	50	3.77	43	3.13
Blood triglyceride	48.8	17.82	27.2	4.18
Blood VLDL	19.6	3.81	13.4	1.58

Table 3 shows the levels of blood glucose before and after the administration of mad honey for the first 3 days after streptozotocin-induced diabetes mellitus in the experimental group. The treatment with mad honey caused a significant decrease in the blood glucose levels for the first and third days and the mean of the 3 days ($t = 3.45$, $P = 0.01$; $t = 2.35$, $P = 0.04$; $t = 2.42$, $P = 0.04$, respectively).

The blood cholesterol, triglyceride and VLDL levels were 46.4 ± 10.31, 98 ± 43.3 and 19.4 ± 8.07 mg/dl after streptozocin-induced diabetes mellitus but before the administration of mad honey. The blood cholesterol, triglyceride and VLDL levels were 35.8 ± 7.68, 44.6 ± 9.86 and 9 ± 1.76 mg/dl after the mad honey treatment (Table 4). The differences between before and after the administration of mad honey were statistically significant (for cholesterol, $t = 3.92$, $P = 0.004$; for triglyceride, $t = 4.54$, $P = 0.001$; for VLDL, $t = 4.53$, $P = 0.001$).

Discussion

Streptozocin administration to mature rats induces severe and permanent diabetes, with a decrease in insulin levels, to produce a cytotoxic model of diabetes very similar to type I diabetes mellitus. Streptozocin damages B cells of the islets of Langerhans in the pancreas (10).

The blood glucose levels increased progressively from day to day for 3 days in the experimental group. This

Table 3. The levels (mg/dl) of blood glucose before and after the administration of mad honey for the first 3 days and the mean of 3 days after streptozotosin-induced diabetes mellitus in the experimental group (N = 10).

	Before treatment		After treatment	
Parameters	Mean	SD	Mean	SD
Blood glucose (the first day)	239.2	39.57	183	78.85
Blood glucose (the second day)	317.8	91.04	247.2	61.61
Blood glucose (the third day)	415.6	120.99	365	56.23
Blood glucose (The mean of 3 days)	324.2	72.16	267.73	48.89

Table 4. The levels (mg/dl) of blood cholesterol, triglyceride and VLDL before and 3 days after the administration of mad honey in the experimental group (N = 10).

	Before treatment		After treatment	
Parameters	Mean	SD	Mean	SD
Blood cholesterol	46.4	10.31	35.8	7.68
Blood triglyceride	98	43.3	44.6	9.86
Blood VLDL	19.4	8.07	9	1.76

suggests that the damage by streptozocin on B cells of the islets of Langerhans in the pancreas increases progressively.

Onat et al. (7) reported that grayanotoxin-contaminated honey extract was not bradycardic in bilaterally vagotomized animals. They suggest that the sites of cardiac and respiratory actions are within the central nervous system, and that the bradycardic effect of grayanotoxin is mediated by vagal stimulation at the periphery. In another study (8), the same researchers reported that atropin sulfate improved both bradycardia and respiratory rate depression. AF-DX 116, which is a selective M_2-muscarinic receptor antagonist, restored heart rate, but not the respiratory rate depression, and they claimed that M_2-muscarinic receptors are involved in the cardiotoxicity of grayanotoxins.

In this study, it was found that the mad honey caused significant decreases in blood glucose and lipid (cholesterol, triglyceride and VLDL) levels in both groups. These decreases may be due to grayanotoxins in the mad honey.

The effects of grayanotoxins are mediated by the parasympathetic nervous system and M_2-muscarinic receptor stimulation. It is well known that the stimulation of the parasympathetic nervous system or M_2-muscarinic receptors increases insulin secretion by the pancreas (11). In the light of these findings, it can be stated that grayanotoxins or mad honey decrease the blood glucose and lipids by secreting insulin from the islets of Langerhans in the pancreas by stimulating the parasympathetic nervous system or M_2-muscarinic receptors.

In conclusion, mad honey decreases blood glucose and lipid levels. Most likely this effect is due to the stimulation of grayanotoxins on the parasympathetic nervous system. The results of this study suggest that mad honey in small doses can be used as a dietary supplement, especially by patients with type II diabetes mellitus, because B cells of the islets of Langerhans in the pancreas can secrete insulin in patients with type II diabetes mellitus.

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