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Anti-diabetic activity of diphenhydramine in diabetic rats

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ABSTRACT

The purpose of this project is to study the anti-diabetic effect of diphenhydramine on a diabetic rat model. A total of Twenty male Sprague Dawley rats were used and it randomly distributed into four groups which are Group I: Glibenclamide, Group II: negative control, Group III: Diphenhydramine and Group IV: Diphenhydramine and Glibenclamide. In vivo diabetic model were induced with Streptozocin via intraperitoneal injection at the dosage of 65mg/kg. Bodyweight and FBG (Fasting Blood Glucose) level of diabetic rats were assessed every three days. Blood was collected via cardiac puncture at day 21 after the induction of treatment. Insulin level of the rats was assessed with the Mercodia Rat Insulin ELISA kit. FBG level of group I (12.16 $\pm$3.96, $p<0.05$) and group IV (11.34 $\pm$3.67, $p<0.05$) were significantly decreased. Meanwhile, the bodyweight for all rats did not show any significant increase. However, the insulin level was escalated in group IV (0.74+0.25, $p<0.05$) significantly. The present study shows that the diphenhydramine and the combination of diphenhydramine and glibenclamide lowered blood glucose level and enhanced insulin secretion.

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INTRODUCTION

Based on the estimation by the World Health Organization (Zheng *et al.*, 2018), more than 350 million people will have diabetes. This number is predicted to increase in double by the next decade. Statistic showed that 80% of diabetes deaths occurred in developing countries. Diabetes also categorises as a non-communicable disease which is one of the diseases that leads to cause of mortality in the world. This epidemic disease has to hinder the development of poverty countries. The burden of those poverty countries was growing with the number of people and communities afflicted.

The complexity of diabetes disease increases the risk of the patient for many serious health problems. It can affect each part of the body, including the skin. Allergy is one of the common skin diseases faced by diabetes patient (Feitosa *et al.*, 2013). Because of that, the antihistamine drug was always found in diabetes patient prescription. Chosen the right antihistamine drug is essential because most of the drugs could affect the blood glucose level and give an adverse effect on the patient.

Antihistamines were a drug that is used to alleviate itching. Itching could lead to the development of eczema by weeping and thickening the skin. Generally, eczema becomes worse and could be infected due to scratching that break the skin. Besides that, antihistamine drug was also commonly used to treat allergies such as hay fever (Bebarta *et al.*, 2010; Chiavegatto *et al.*, 1997).

Studies have stipulated that antihistamine drug, diphenhydramine hydrochloride (diphenhydramine), ameliorate retinal barrier in vivo diabetic model (Enea, 1989). However, its mechanism

on streptozotocin-induced rats is still unknown. Thereby, this study is an attempt to inquire about the anti-diabetic effect of antihistamine drug, diphenhydramine hydrochloride in diabetic rats.

MATERIALS AND METHODS

Animals

The study was conducted on 20 male Sprague-Dawley rats (200-250g). Animals were kept on a natural day-night cycle (12 hours dark; 12 hours light) at room temperature of 26-27°C.

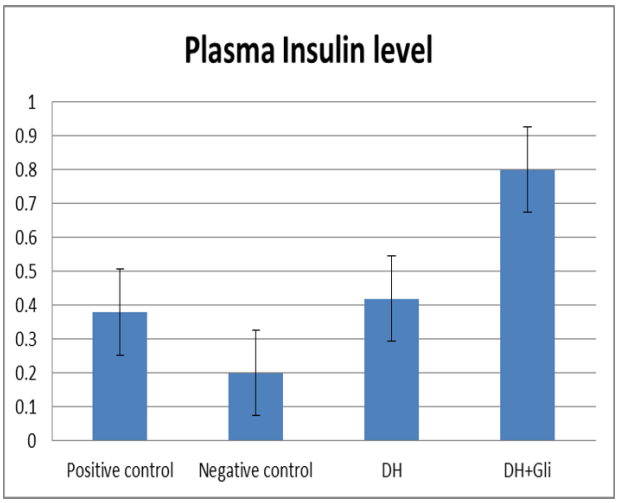

Figure 1: Plasma insulin level of diabetic rats. (p<0.05).

Induction of Diabetes

A streptozotocin-induced hyperglycemic rat was used as an animal model of diabetes. Streptozocin was purchased from Santa Cruz (cat no: 4-9889, SC-200719) and 65mg/kg per rats was used to induce animal diabetic model. The streptozocin was diluted with citrate buffer (0.1 M at pH 4.5) and was administrated into rats body intraperitoneally. Blood was collected from the vein and assessed its blood glucose level 3 days after the initial injection of streptozocin. Animals with FBG level more than 6.0 mmol/L (concentration: 120 to 250 mg/dL) was considered as diabetic (Zainah *et al.*, 2007).

Investigation of Anti-diabetic Activity

Twenty-five male Sprague-Dawley rats were divided into four groups, with each group consists of 5 rats. Rats were acclimatised for one week under a 12/12 hour ratio for light and dark cycle. Group I was classified as a positive control in which rats were treated with 0.5 mL glibenclamide, group II as a negative control in which rats were given distilled water, group III as treated group in which rats were given 0.5 mL diphenhydramine and group IV as a treated group in which rats were given 0.25 mL diphenhydramine and 0.25 mL glibenclamide.

Insulin ELISA Test

Mercodia Rat Insulin ELISA (ALPCO diagnostics Lmt (co)) was used to measure the insulin level of all rats. The insulin ELISA test was conducted according to the manufacturer manual, Mercodia ELISA kit manual.

Blood Glucose Test

Blood glucose level was assessed on every three days basis for 21 days. It was measured with an electronic glucometer (Accu-check advantage, Roche Diagnostic, Germany) was used to measure diabetic rats blood glucose level.

Statistical Analysis

The ANOVA test was employed to all data for factorial comparison and LSD(Least Significant Test) test for multiple comparisons. Data were considered significant at p <0.05.

RESULTS AND DISCUSSION

Influence of Glibenclamide and Diphenhydramine on diabetic rats glucose level

Diabetic rat's FBG level had decreased significantly for rats in group I (Mean+SEM; 11.34+3.67, p<0.017) and group IV (Mean+SEM; 12.16+3.96, p<0.023) (Table 1). The FBG level in group I and group IV had significant decrease might be because of the glibenclamide effect. Glibenclamide is the second generation of the Sulfonylureas, and it is the oral hypoglycaemic drugs which are used routinely for diabetes treatment.

Effect of Glibenclamide and Diphenhydramine on body weight

Measurement of rats body weight was taken every three days. It shows that the bodyweight of the rats was not significantly increased in all diabetic rats. However, there was a pattern of increasing body weight during the experiment. The body weight was higher in positive groups, Group I and treatment groups (group II and group III) compared to the negative control (Table 2).

Generally, the bodyweight of group I rats, positive control and treatment group, group III and group IV, increased. This might be due to the consumption of glibenclamide which can cause weight gain in diabetic rats (Azmi and Qureshi, 2012).

According to previous research, the consumption of diphenhydramine in the body could cause loss of body weight or anorexia due to loss in appetite (Carlson *et al.*, 2000; Hung *et al.*, 2011; Sadiq *et al.*, 2011).

Table 1: Changes of FBG Level after Treatment Induction

Group	FBG Level measurement (mmol/L)					
	FBGL 1	FBGL 2	FBGL 3	FBGL 4	FBGL 5	FBGL 6
I (Positive control)	14.28 ±0.83	21.48 ±3.57	21.86 ±5.28	19.08 ±4.74	15.70 ±4.59	11.34 ±3.67*
II (Negative control)	12.58 ±1.68	16.22 ±2.53	22.52 ±2.36	20.48 ±4.44	21.18 ±3.79	25.06 ±3.35
III (Diphenhydramine)	18.70 ±1.99	23.74 ±3.12	25.34 ±3.66	11.40 ±3.20	23.26 ±2.07	18.64 ±3.55
IV (Diphenhydramine+Glibenclamide)	20.70 ±3.43	9.64 ±1.85	26.58 ±4.77	11.32 ±3.19	17.06 ±3.53	12.16 ±3.96*

Datapresented as Mean ± SEM; n=5. * p <0.05 = significant.

Table 2: Changes in Body Weight after Treatment Induction

Group	Body Weight measurement (g)					
	BW 1	BW 2	BW 3	BW 4	BW 5	BW 6
I (Positive control)	179.99 ±4.77	195.42 ±13.82	196.27 ±15.77	209.16 ±19.42	215.59 ±19.79	210.85 ±22.67
II (Negative control)	181.08 ±4.03	192.27 ±14.10	191.77 ±15.73	198.17 ±17.99	202.91 ±17.71	204.46 ±20.24
III (Diphenhydramine)	165.63 ±6.33	167.65 ±13.03	164.92 ±14.73	174.51 ±18.35	180.09 ±18.74	176.33 ±22.53
IV (Diphenhydramine+Glibenclamide)	199.79 ±11.81	215.82 ±20.46	222.98 ±20.38	226.66 ±23.99	231.32 ±24.05	224.93 ±26.97

*Data stated as Mean ± SEM; n=5.

However, the result of this study showed that the administration of diphenhydramine increased the bodyweight of diabetic rats. Besides that, glibenclamide was metabolised in the liver for about 4 to 6 hours (Tripathi, 2003).

According to Rai *et al.* (2012), glibenclamide provokes insulin secretion from β-cell by impeding ATP sensitive K^+ channels in the plasma membrane hence, leads to the elevation of voltage-gated Ca^{2+} channels and increased Ca^{2+} influx depolarisation which finally increased insulin secretion. Thus, the FBG level decreases in diabetic rats.

Based on the observation, group IV (glibenclamide dosage had been reduced to half of the dosage of group I), showed similar FBG level as group I. We hypothesise the reducing of group IV FBG level might be caused by the induction of diphenhydramine in ß-cell of Langerhans to increase secretion of insulin. Besides that, studies that have been done by Arun *et al.* (2012) proven Bromelain, an agent of inhibiting allergy sensitisation, possess anti-diabetic activity on streptozotocin-induced diabetic rats.

Effect of Glibenclamide and Diphenhydramine on Insulin Level

Insulin level in the rat plasma was found significantly higher in the treatment group; group IV, (mean+SEM (0.74+0.25)) compare with treatment group III; (0.38+0.07), the group I, positive control (0.33+0.03) and group II, negative control (0.32+0.02) (Figure 1). Positive control – treated with Glibenclamide, Negative control – distilled water, DH – Diphenhydramine Chloride, DH+Gli – Diphenhydramine Chloride + Glibenclamide.

From the result of the FBG level in diabetic rats, further investigation was carried out on the possibility of diphenhydramine increase secretion of insulin in pancreatic ß-cells. We found that plasma insulin level in group IV was higher compared to the other groups. According to León-Reyes *et al.* (2008), glibenclamide is used to increase insulin secretion in diabetes patient due to their direct action on pancreatic β-cells. In this study, it was found that rats treated with glibenclamide, the group of rats that treated with diphenhydramine were also having increased of insulin secretion.

CONCLUSION

This study reports that diphenhydramine reduced FBG level and increased insulin secretion in

streptozotocin-induced diabetic rats. Meanwhile, the body weight of diabetic rats gradually increased together with the increased secretion of insulin level. Hence, diphenhydramine has the effect of lowering the FBG level by increasing insulin level in diabetic rats. However, in another group of experimental rats, plausible of diphenhydramine with glibenclamide as a synergic treatment on diabetic rats need to be further investigated especially on the morphological changes of pancreas and its toxicity effect after the induction of diphenhydramine and glibenclamide.

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Conflict of interest

The authors declare that they have no conflict of interest for this study.

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