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AMELIORATION OF OLANZAPINE-INDUCED IMPAIRED GLUCOSE TOLERANCE IN MICE WITH METHANOL EXTRACT OF STEAMED *Brassica oleracea* (CABBAGE) LEAVES

FARJANA AKTHER NOOR[1], SONGJUKTA CHAKRABORTY[2], CHRISTOPHE WIART[3] AND MOHAMMED RAHMATULLAH[2]*

[1]Department of Biotechnology & Genetic Engineering,
University of Development Alternative, Dhaka, Bangladesh
[2]Department of Pharmacy, University of Development Alternative, Dhaka, Bangladesh
[3]School of Pharmacy, University of Nottingham Malaysia Campus, Semenyih, Malaysia

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Olanzapine is an antipsychotic drug and has been reported to induce impaired glucose tolerance leading to high blood glucose levels. In oral glucose tolerance tests (OGTT), methanolic extract of steamed cabbage (Brassica oleracea L. var. capitata) (MEBO) leaves have been shown to reduce elevated blood glucose levels in glucose-loaded mice. It was thus of interest to determine whether MEBO leaves can ameliorate olanzapine-induced impaired glucose tolerance in mice, which have been administered olanzapine for 28 days. Impaired glucose tolerance was measured through OGTT in mice. Olanzapine (28 days)-administered mice showed elevated blood glucose in OGTT. MEBO leaves showed significant reduction of blood glucose level in OGTT in mice (compared to vehicle or olanzapine treated mice for 28 days, Groups 2 and 3, respectively) both when administered for 28 days along with olanzapine, as well when administered 60 min prior to glucose loading in OGTT (positive control glibenclamide administered at 10 mg/kg). A single dose of MEBO (400 mg/kg) was used based on previous studies. Thus, MEBO leaves can be beneficial for improving glucose tolerance and reduce blood glucose levels in olanzapine-induced elevated blood glucose levels.

Keywords: Olanzapine, OGTT, Cabbage, Mice

INTRODUCTION

Type 2 diabetes mellitus and impaired glucose tolerance are associated with antipsychotic treatment. The strength of the association between antipsychotics and impaired glucose tolerance varies across individual medications, with the largest number of reports for

*Corresponding author: rahamatm@hotmail.com

chlorpromazine, clozapine, and olanzapine (Haupt and Newcomer 2001). In a previous study we have shown that chronic oral administration of olanzapine (100 mg/kg body weight for 28 days) can induce glucose intolerance in mice (Noor, Hossain and Rahmatullah 2016). In another study it has been shown that methanol extract of steamed *Brassica oleracea* L. var. *capitata* (cabbage) (MEBO) leaves can improve glucose tolerance in glucose-loaded mice, and so lower blood glucose levels in oral glucose tolerance test or OGTT (Akther *et al.* 2016). It was, thus, of interest to evaluate the potential of MEBO to ameliorate glucose intolerance induced by olanzapine in mice.

METHODS

Chemicals and Drugs

Olanzapine was obtained from Sigma Chemical Co., USA; glibenclamide and glucose were obtained from Square Pharmaceuticals Ltd., Bangladesh. All other chemicals were of analytical grade. Methanol and dimethyl sulfoxide (DMSO) were obtained from Merck (Germany). Olanzapine was dissolved in DMSO prior to oral gavaging in mice.

Animals

Swiss albino mice, which weighed between 15 g and 19 g were used in the present study. The animals were obtained from the International Centre for Diarrhoeal Disease Research (ICDDR), Bangladesh. The animals were acclimatised for 3 days prior to actual experiments; the actual experiments were conducted over a period of 4 weeks where the mice were supplied with normal mice chow (obtained from ICDDR, B) and water *ad libitum*. Experimental mice received olanzapine dissolved in 1% DMSO by gavaging every day during this time period (4 weeks).

Collection of Cabbage and Preparation of Leaf Extract

Cabbage was bought from a local market in Dhaka, Bangladesh. The plant was identified at the Bangladesh National Herbarium with accession number of 39513. MEBO leaves were done as described earlier.

Oral Glucose Tolerance Tests

OGTT were carried out as previously described (Joy and Kuttan 1999). Briefly, mice were grouped into 6 groups of 5 mice each (Groups 1–6) and OGTT was performed on Groups 2–6 mice. The various groups received different treatments like Group 1 received just mice chow and water *ad libitum* for 28 days. Group 1 mice were fasted for 16 h after 28 days and then sacrificed followed by measurement of blood glucose (considered as fasting basal blood glucose level). Groups 2–6 mice received mice chow and water *ad libitum* for 28 days. Group 2 also received vehicle (1% DMSO) during this 28 day time period and served as control. Groups 3–6 received olanzapine (100 mg/kg body weight/day) for the same time period (28 days). Group 4 mice received MEBO (400 mg per kg body weight/day) additionally with olanzapine. After 28 days, Groups 2–6 mice were fasted for 16 h followed by administration of vehicle (Groups 2–4), glibenclamide (10 mg/kg body weight) to Group 5 and MEBO (400 mg/kg body weight) to Group 6. In the experiment, a

single dose of MEBO (400 mg/kg) was used based on previous studies (Akther *et al*. 2016). All substances, i.e. vehicle, glibenclamide and extract (MEBO) were orally administered. Following a period of 1 h, Groups 2–6 mice were orally administered 2 g glucose/kg of body weight. Blood glucose levels were measured 120 min after glucose administration with a glucometer (Islam *et al*. 2009). The percent lowering of blood glucose levels were calculated according to the formula described below.

$$\text{Percent lowering of blood glucose level} = (1 - W_e/W_c) \times 100,$$

where W_e and W_c represents the blood glucose concentration in experimental (Groups 3–6) mice and control mice (Group 2), respectively.

Statistical Analysis

Experimental values are expressed as mean ± SEM. Independent sample *t*-test was carried out for statistical comparison. Statistical significance was considered to be indicated by a *p*-value < 0.05 in all cases (Hossain *et al*. 2014).

Ethical Approval

The study was conducted following approval by the Institutional Animal Ethical Committee of University of Development Alternative, Dhaka, Bangladesh.

RESULTS

At the end of 28 days, Group 1 mice had blood glucose levels of 4.16 ± 0.37 mmol/L (fasting basal blood glucose level, mean ± SEM). In OGTT tests, Group 2 (that is glucose-loaded control mice) had elevated blood glucose levels of 5.80 ± 0.16 mmol/L. In Group 3 (olanzapine administered for 28 days), mice in OGTT demonstrated blood glucose levels of 7.30 ± 0.15 mmol/L, that is a 25.9% increase over Group 2 control mice (significant at $p < 0.05$), in agreement with previous studies that chronic intake of olanzapine causes impaired glucose tolerance leading to elevated blood glucose levels (Noor, Hossain and Rahmatullah 2016). In Group 4 (olanzapine along with MEBO administered for 28 days), mice in OGTT tests showed blood glucose levels of 4.72 ± 0.21 mmol/L, suggesting that MEBO can ameliorate olanzapine-induced impaired glucose tolerance (Group 4 versus Group 3). Administration of glibenclamide (Group 5) or MEBO (Group 6) led to reductions of blood glucose levels in OGTT by 39% and 34.8%, respectively. The results are shown in Table 1 and suggest that MEBO can possibly be as effective as an antihyperglycemic drug, glibenclamide in restoring impaired glucose tolerance and consequent hyperglycemia caused by olanzapine.

Table 1: Effect of MEBO on blood glucose levels in OGTT in mice with olanzapine-induced elevated blood glucose levels.

Experimental details	Treatment and dose (mg/kg body weight)	Blood glucose level (mmol/L)	% Change in blood glucose level
Group 1 (fasting basal blood glucose)	Vehicle (28 days)	4.16 ± 0.37	Not applicable
Group 2 (OGTT)	Vehicle (28 days)	5.80 ± 0.16	0
Group 3 (OGTT)	100 mg olanzapine (28 days)	7.30 ± 0.15	+25.9*
Group 4 (OGTT)	100 mg olanzapine (28 days) + 400 mg MEBO (28 days)	4.72 ± 0.21	–18.6*
Group 5 (OGTT)	100 mg olanzapine (28 days) + glibenclamide (10 mg/kg, 1 h before glucose administration)	3.54 ± 0.13	–39.0*
Group 6 (OGTT)	100 mg olanzapine (28 days) + MEBO (400 mg/kg, 1 h before glucose administration)	3.78 ± 0.06	–34.8*

Notes: All administrations were made orally. Values represented as mean ± SEM, (n = 5); *p < 0.05; significant compared to hyperglycemic control animals (Group 2).

DISCUSSION

It is to be noted that since MEBO was efficient in lowering olanzapine-induced elevated blood glucose level in mice in the present study, it is possible that it may prove beneficial to patients undergoing treatment with olanzapine. Cabbage is known to contain β-sitosterol, chlorogenic acid, ferulic acid, kaempferol and quercetin (Duke 1992). It is worthwhile to explore the effects of these individual ingredients in olanzapine treated mice, for a number of these compounds have reported blood glucose lowering efficacies (Oboh *et al.* 2015; Varghese, Bose and Habtemariam 2013; Karan *et al.* 2012; Alkhalidy *et al*. 2015; Aguirre *et al.* 2011).

CONCLUSION

Cabbage leaves may be potential sources of new drugs to improve impaired glucose tolerance.

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