J. Pharm. Pharmacol. 1999, 51: 741–743
Received September 22, 1998
Accepted January 26, 1999

Effect of Some Antidepressants on Glycaemia and Insulin Levels of Normoglycaemic and Alloxan-induced Hyperglycaemic Mice

A. ERENMEMISOGLU, U. K. OZDOGAN, R. SARAYMEN* AND A. TUTUS†

*Departments of †Biochemistry and *Pharmacology, Nuclear Medicine, Faculty of Medicine, Erciyes University, 38039 Kayseri, Turkey*

Abstract

Depression is an important problem among diabetic patients. We have investigated the effect of some antidepressant drugs on plasma glucose and insulin levels in normoglycaemic and alloxan-induced diabetic mice. For this purpose the effects of nortryptiline (as an example of a tricyclic antidepressant) and fluoxetine and sertraline (as examples of selective 5-HT re-uptake inhibitors) were examined on plasma glucose and insulin levels.

Nortryptiline significantly increased glucose levels and reduced insulin levels in all animals. Although neither fluoxetine nor sertraline induced changes in insulin levels, both significantly reduced the blood glucose levels of mice.

These results suggest that antidepressive treatment has important risks particularly for diabetics. Tricyclic antidepressants might induce an important decrease in glucose tolerance and worsen the control of diabetic patients. Selective 5-HT re-uptake inhibitors, on the other hand, might reduce plasma glucose independently of insulin levels. This point is particularly important and should be remembered when insulin or oral antidiabetic agents are administered to diabetics, because of the possible risk of hypoglycaemia.

Studies have shown that depression is an important problem in diabetic patients (Goodnick et al 1995; Goodnick 1997). In controlled studies, rates of depression in diabetes mellitus have ranged from 8·5 to 27·3% (Goodnick 1997). It has been reported that tricyclic antidepressants elevate blood glucose levels and reduce plasma insulin (Kaplan et al 1960; Katz et al 1991; Goodnick et al 1995; El-Dakhakhny et al 1996) and that some increase the plasma levels of free fatty acids (El-Dakhakhny et al 1996).

Selective 5-HT re-uptake inhibitors might cause hypoglycaemia (causing as much as a 30% decrease in fasting plasma glucose) and anorexia (Furman 1974; Furman & Wilson 1980; El-Dakhakhny et al 1996). However, it has been suggested that 5-HT might act to reduce plasma glucose independently of insulin secretion (Wilson & Furman 1982; Goodnick et al 1995). In summary, antidepressive treatment (monoaminooxidase inhibitors included) might induce significant changes in the plasma glucose levels of patients.

In this study we have investigated the effect of tricyclic antidepressants and selective 5-HT re-uptake inhibitors on the plasma glucose and insulin levels of normoglycaemic and alloxan-induced diabetic mice.

Correspondence: A. Erenmemisoglu, Department of Pharmacology, Faculty of Medicine, Erciyes University, 38039 Kayersi, Turkey.

Materials and Methods

Animals

Sixty-four adult Swiss albino mice of either sex, 20–30 g, were used in the experiments. Animals had free access to standard laboratory chow and water; they were maintained in a 12-h dark–light cycle.

Normoglycaemic mice

Thirty-two mice were separated into four equal groups of eight. One, the control group, received saline (0·3 mL saline/30 g mouse). Fluoxetine (Lily), sertraline (Pfizer) or nortryptiline (Sigma) was administered to the other groups ($30\,mg\,kg^{-1}$/day).

Alloxan-induced hyperglycaemic mice

Thirty-two mice were made diabetic by means of a single intraperitoneal injection of 75 mg kg^{-1} alloxan monohydrate (Merck; Erenmemisoglu et al 1995). Alloxan was administered intraperitoneally at the low dose to induce mild hyperglycaemia and avoid extremely low plasma insulin concentrations. Seven days after alloxan injection urine was collected from all animals and evaluated by use of glucose test strips (Macherey-Nagel). The mice were divided into four equal groups. One was the control; the others received fluoxetine, sertraline and nortryptiline (as described for normoglycaemic mice).

Experimental procedure

All groups received the drugs for 21 days. Drugs were dissolved in saline (0·3 mL/30 g mouse) and administered by single intraperitoneal injection. Mice were fasted for 18 h at the end of the study, blood samples were obtained after decapitation and plasma was separated for analysis of blood glucose and insulin levels.

Analytical procedure

Plasma glucose and insulin levels were determined for all groups. Plasma glucose was measured by the glucose oxidase method (Diasys) and insulin level by radioimmunoassay with a commercially available kit (Coat-a-count) with insulin from man as the standard.

Statistics

Data are expressed as means ± s.e.m. One-way analysis of variance and modified *t*-tests were used to evaluate the significance of results from all the experiments (Wallenstein et al 1980). $P < 0{\cdot}05$ was considered to be indicative of statistical significance.

Results

The antidepressant drugs caused important changes in the blood glucose levels of the animals. Nortryptiline (as an example of a tricyclic antidepressant) significantly increased the blood glucose levels of normoglycaemic and alloxan-induced hyperglycaemic mice ($P < 0{\cdot}05$ and 0·001 respectively) compared with controls. Nortryptiline also significantly reduced the insulin levels of normoglycaemic and alloxan-induced hyperglycaemic mice ($P < 0{\cdot}01$). The results are presented in Tables 1 and 2 . The blood glucose and insulin levels of the normoglycaemic group were different from those of the alloxan-induced hyperglycaemic animals ($P < 0{\cdot}01$).

Table 1. The effect of antidepressant drugs on plasma glucose and insulin levels in normoglycaemic mice.

Normoglycaemic mice	Plasma glucose level (mg dL^{-1})	Plasma insulin level (μUnits mL^{-1})
Control	133·57 ± 6·9	17·93 ± 1·62
Nortryptiline	159·90 ± 6·19*	10·31 ± 0·51*
Sertraline	96·87 ± 5·59**	17·68 ± 0·96
Fluoxetine	99·57 ± 5·34**	17·47 ± 1·51

Results are means ± s.e.m., n = 8 for each group. *$P < 0{\cdot}01$, **$P < 0{\cdot}05$ compared with control.

Table 2. The effect of antidepressant drugs on plasma glucose and insulin levels in alloxan-induced hyperglycaemic mice.

Alloxan-induced hyperglycaemic mice	Plasma glucose level (mg dL^{-1})	Plasma insulin level (μUnits mL^{-1})
Control	233·75 ± 8·30	6·13 ± 0·61
Nortryptiline	274·87 ± 11·64*	3·50 ± 0·44*
Sertraline	196·87 ± 6·02**	6·10 ± 0·49
Fluoxetine	191·75 ± 7·53**	5·78 ± 0·52

Results are means ± s.e.m., n = 8 for each group. *$P < 0{\cdot}01$, **$P < 0{\cdot}05$ compared with control.

Fluoxetine and sertraline (as examples of selective 5-HT re-uptake inhibitors) had no effect on the insulin levels of normoglycaemic or alloxan-induced hyperglycaemic mice but induced a significant reduction in the blood glucose levels of both groups ($P < 0{\cdot}01$). These results are also presented in Tables 1 and 2 . No difference was found between the effects of sertraline and fluoxetine on blood glucose and insulin levels of mice ($P > 0{\cdot}05$) (Tables 1 and 2).

Discussion

Diabetes mellitus can be associated with depression, which can have a more malevolent course in diabetics. The relapse rate is eight times greater in diabetic depressed patients than in a depressed but physiologically healthy population (Lustman et al 1988). This becomes particularly important in the treatment of diabetes mellitus because of the negative influences both of diabetes on major depression and of major depression on diabetes mellitus (Goodnick 1997). Antidepressive treatment might induce metabolic changes in patients and this might be especially important for diabetics.

According to our data, nortryptiline significantly increased blood glucose levels and significantly reduced insulin levels in all groups. These two results are in agreement with literature results (Goodnick et al 1995; El-Dakhakhny et al 1996). Despite these metabolic effects of nortryptiline, blood glucose and insulin levels of the nortryptiline administered normoglycaemic group were different from those of nortryptiline-administered hyperglycaemic animals. In other words, normoglycaemic mice were not made diabetic by nortryptiline and their blood glucose levels were normal but near the upper limits (Canadian Council and Animal Care 1984). It is well known that tricyclic antidepressants have relatively more effect on re-uptake of noradrenaline than of 5-HT. The principal effect of tricyclic antidepressants on the function of the autonomic nervous system is believed to result from inhibition of noradrenaline transport into adrenergic nerve terminals and from antagonism of muscarinic cholinergic and α_1 adrenergic neurotransmitters (Baldessarini 1990). Increase in catecholamine function seems to increase gluconeogenesis and block insulin release (Goodnick 1997). It has been reported that nortryptiline was not beneficial for hyperglycaemic control in diabetics and was associated with worsening of diabetes, despite having an effective antidepressant effect (Goodnick et al 1995; Goodnick 1997). Tricyclic antidepressants have been used effectively in the treatment of diabetic neuropathy at lower doses than needed for depression (Goodnick 1997). Thus, our data are as expected.

Selective 5-HT re-uptake inhibitors reduced plasma glucose independent of insulin levels in both normoglycaemic and alloxan-induced hyperglycaemic mice. These data were also in agreement with previous work. According to these reports selective 5-HT re-uptake inhibitors can lead to improvement in both depression and glucose control (Wilson & Furman 1982; Goodnick et al 1995). As indicated previously, 5-HT precursors and re-uptake inhibitors seem to be associated with hypoglycaemia (Furman 1974; Furman & Wilson 1980; Wilson & Furman 1982). These studies suggest the presence of a non-insulin-related effect of 5-HT on glucose regulation. The mechanism of this effect is not yet clear.

The individual effects of tricyclic antidepressants and selective 5-HT re-uptake inhibitors on the biochemical parameters measured were no different in normoglycaemic and alloxan-induced hyperglycaemic mice. These results suggest that tricyclic antidepressants might induce important metabolic changes in patients. There might, therefore, be a risk in the use of these agents, especially in the treatment of diabetic depressed patients. Tricyclic antidepressants might occasionally induce a reduction in glucose tolerance and a predisposition to hyperglycaemia (e.g. occurrence of obesity). It is well known that tricyclic antidepressants lead to weight gain whereas selective 5-HT re-uptake inhibitors usually lead to weight loss (Goodnick 1997). As is apparent from the results discussed above, selective 5-HT re-uptake inhibitors can reduce plasma glucose. This point is also particularly important and, in our opinion, should be remembered when insulin or other oral antidiabetic agents are administered to diabetics because of the possible hypoglycaemia risk. Hypoglycaemia risk might also be valid for non-diabetic depressed patients, especially when selective 5-HT re-uptake inhibitors are ingested before meals. In our opinion selective 5-HT re-uptake inhibitors seem more suitable than tricyclic antidepressants for treatment of diabetic depressed patients. These data should be confirmed by studies with man.

References

Baldessarini, R. J. (1990) Drugs and the treatment of psychiatric disorder. In: Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F. (eds) The Pharmacological Basis of Therapeutics, 8th edn, Pergamon Press, New York, pp 383–435

Canadian Council and Animal Care (1984) Guide to the Care and Use of Experimental Animals, CCAC, Ottawa

El-Dakhakhny, M., Hekmat, A., El-Latif, A. (1996) Different effects of the antidepressant drugs: imipramine, maprotiline and bupropion on insulin secretion from mouse pancreatic islets. Arzneim. Forsch. 46: 667–669

Erenmemisoglu, A., Kelestimur, F., Koker, A. H., Ustun, H.,Tekol, Y., Ustal, M. (1995) Hypoglycaemic effect of *Zizyphus jujuba* leaves. J. Pharm. Pharmacol. 47: 72–74

Furman, B. L. (1974) The hypoglycaemic effect of 5-hydroxytryptophan. Br. J. Pharmacol. 50: 575–580

Furman, B. L., Wilson, G. A. (1980) Further studies on the effects of 5-hydroxytryptophan on plasma glucose and insulin in the mouse. Diabetologia 19: 386–390

Goodnick, P. J. (1997) Practical considerations in the treatment of depression in the diabetic patient. Primary Psychiatr. 4: 37–40

Goodnick, P. J., Henry, H. J., Buki, M. V. M. (1995) Treatment of depression in patients with diabetes mellitus. J. Clin. Psychiatr. 56: 128–136

Kaplan, S. M., Maas, J. W., Pixley, J. M. et al (1960) Use of imipramine in diabetics. J. Am. Med. Assoc. 174: 511–517

Katz, L. M., Fochtman, L. F., Pato, M. T. (1991) Clomipramine, fluoxetine and glucose control. Ann. Clin. Psychiatr. 3: 271–274

Lustman, P. J., Griffith, L. S., Clouse, R. E. (1988) Depression in adults with diabetes. Diabetes Care 11: 605–612

Wallenstein, S., Zucker, C. L., Fleiss, J. L. (1980) Some statistical methods useful in circulation research. Circ. Res. 47: 1–9

Wilson, G. A., Furman, B. L. (1982) Effects of inhibitors to 5-hydroxytryptamine uptake on plasma glucose and their interaction with hydroxytryptophan in producing hypoglycemia in mice. Eur. J. Pharmacol. 78: 263–270