

Acute effect of different antidepressants on glycemia in diabetic and non-diabetic rats

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Abstract

Diabetic patients have a 20% higher risk of depression than the general population. Treatment with antidepressant drugs can directly interfere with blood glucose levels or may interact with hypoglycemic agents. The treatment of depression in diabetic patients must take into account variations of glycemic levels at different times and a comparison of the available antidepressant agents is important. In the present study we evaluated the interference of antidepressants with blood glucose levels of diabetic and non-diabetic rats. In a first experiment, male adult Wistar rats were fasted for 12 h. Imipramine (5 mg/kg), moclobemide (30 mg/kg), clonazepam (0.25 mg/kg), fluoxetine (20 mg/kg) sertraline (30 mg/kg) or vehicle was administered. After 30 min, fasting glycemia was measured. An oral glucose overload of 1 ml of a 50% glucose solution was given to rats and blood glucose was determined after 30, 60 and 90 min. Imipramine and clonazepam did not change fasting or overload glycemia. Fluoxetine and moclobemide increased blood glucose at different times after the glucose overload. Sertraline neutralized the increase of glycemia induced by oral glucose overload. In the second experiment, non-diabetic and streptozotocin-induced diabetic rats were fasted, and the same procedures were followed for estimation of glucose tolerance 30 min after glucose overload. Again, sertraline neutralized the increase in glycemia after glucose overload both in diabetic and non-diabetic rats. These data raise the question of whether sertraline is the best choice for prolonged use for diabetic individuals, because of its antihyperglycemic effects. Clonazepam would be useful in cases with potential risk of hypoglycemia.

Key words

- Depression
- Antidepressants
- Glucose tolerance
- Diabetes
- Glycemia

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Introduction

Diabetes mellitus is a common chronic disease. Its prevalence varies in different countries, corresponding to 10% of the general American population (1) and 7% of the Brazilian population (2). Its damaging effects on the central nervous system, heart,

eyes, kidneys, vascular system and peripheral nerves and the beneficial effects of glucose homeostasis by diabetes treatment to prevent them are well known (1,3). Pharmacological treatments must be added to prevent or to treat peripheral organ problems.

There is a high incidence of depression in insulin-dependent and non-insulin-depend-

ent diabetic patients. The risk is 15 to 20% greater than the risk for the general population (4-6). There is a possibility that this percentage is even higher, because depression is underdiagnosed and untreated in many diabetic patients (5,7,8). Depression occurs earlier in life for diabetic patients. In the general population depression signs are present around ages 27 and 35 years, while diabetic patients are depressed by the age of 22 years (9).

The symptoms of depression most commonly related to diabetes are weight loss, psychomotor retardation and tiredness, hypersomnia, feelings of worthlessness, and diminished sexual drive (5). Depression in diabetic patients is proposed to be a result of the changes in life style (diet restriction, chronic treatment, increase in financial expenses, increase in hospitalization frequency) or might be related to physiological changes (blindness, impotence, cognitive damage) (7,10-12). Hyperglycemia may lead to imbalance of the hypothalamo-pituitary-adrenocortical axis and increase cortisol levels, as also observed in depression (13). All of these lines of evidence indicate that depression may be related to diabetes. On the other hand, non-diabetic patients with depressive mood present low glucose tolerance, increased insulin secretion and low sensitivity to insulin (14). Thus, treatment with antidepressant drugs may interfere with blood glucose levels of non-diabetic depressive patients as well as induce changes in blood glucose levels of depressive diabetic individuals.

The treatment of depression is necessary to improve the quality of life of diabetic patients, to increase treatment compliance, and to decrease the risk of microvascular and macrovascular complications (3,7,15,16). Very few studies discuss the effects of antidepressants in diabetic patients (10,17,18). Treatment with antidepressants can directly interfere with blood glucose levels or may interact with hypoglycemic agents. In a re-

cent preclinical study it was demonstrated that prolonged treatment with nortriptyline increases blood glucose in diabetic and non-diabetic mice, while fluoxetine and sertraline decrease it (19). Therefore, treatment with antidepressants for diabetic individuals must consider the variability in blood glucose level control at different times and a comparison of the available antidepressant agents is recommended.

In this study, the acute effects of different antidepressant groups on the glucose tolerance test were evaluated in diabetic and non-diabetic rats.

Material and Methods

Animals

Male adult Wistar rats (N = 162) raised at the Animal House of the Division of Pharmacology and Toxicology, FFCMPA, were maintained in a controlled environment (lights on from 7:00 a.m. to 7:00 p.m. and temperature of $22 \pm 2^\circ\text{C}$) with water and food *ad libitum*. Twelve hours before the experiments, the animals were fasted. All procedures were performed between 12:00 noon and 15:00 h.

Drugs and solutions

Glucose (50%, w/v) was prepared with glucose (D+) glucose monohydrate; Merck S.A., Rio de Janeiro, RJ, Brazil) dissolved in distilled water. One milliliter of this solution was administered to each rat by gavage.

Streptozotocin (60 mg/ml; Sigma Chemical Co., St. Louis, MO, USA) was prepared in phosphate buffer, pH 4.5. Imipramine (5 mg/ml, Tofranil; Biogalênica, São Paulo, SP, Brazil), moclobemide (30 mg/ml, Aurorix; Produtos Roche Químicos e Farmacêuticos S.A., Rio de Janeiro, RJ, Brazil), clonazepam (0.25 mg/ml, Rivotril; Roche), fluoxetine (20 mg/ml, Prozac; Eli Lilly, São Paulo, SP, Brazil) and sertraline (30 mg/ml, Zoloft;

Pfizer, Guarulhos, SP, Brazil) were diluted in distilled water with 0.05% Tween 80 added. The control group received only the vehicle. All solutions were prepared immediately before use. Treatments were administered *ip* in a volume of 1 ml/kg.

Methodology

Experiment 1. Non-diabetic fasted animals were divided into 6 groups and received control solution (CTR, N = 9), 5 mg/kg imipramine (IMI, N = 10), 30 mg/kg moclobemide (MOC, N = 10), 0.25 mg/kg clonazepam (CNZ, N = 10), 20 mg/kg fluoxetine (FLU, N = 10) and 30 mg/kg sertraline (SER, N = 8). Thirty minutes later, blood was collected by puncture of the distal end of the rat tail. The blood drop was applied to the test zone of the strip for immediate measurement of fasting glycemia with a Glucotrend device (Boehringer Institute, Mannheim, Germany). Glucose solution was administered and blood collections were performed every 30 min over a period of 120 min. All rats presenting fasting blood glucose levels above 100 mg/dl were excluded from the sample.

The drug doses were chosen based on their efficacy as antidepressants in previous behavioral studies (20,21).

Experiment 2. In this experiment, animals were divided into two groups: diabetics (STZ, N = 51) and non-diabetics (CTR, N = 51). Streptozotocin (60 mg/kg) was administered *ip* (22) in a single dose 15 days before the experiment. Diabetes was confirmed using glycosuria and hyperglycemia (glycemia higher than 200 mg/dl) as criteria, 72 h after streptozotocin administration (21). All rats not injected with STZ who presented fasting blood glucose levels above 100 mg/dl were excluded from the sample.

Animals from both groups were treated with the same doses as used in experiment 1 for vehicle (N = 8), IMI (N = 9), MOC (N = 10), CNZ (N = 8), FLU (N = 8) and SER (N

= 8) after a 12-h fast. Blood glucose levels were measured during fasting and 60 min after glucose overload as described above, after puncture of the distal end of the rat tail and measurement with a Glucotrend device.

Statistical analysis

The results of each experiment were grouped into a database and analyzed with the Sigma Stat 2.0 Software (Jandel Corporation, San Rafael, CA, USA). Two-way analysis of variance (two-way ANOVA) was applied in experiment 1 considering treatment and time as independent factors and glycemia as the dependent variable. In experiment 2, the effects of diabetic/non-diabetic condition, fasting/overload state and treatment factors on the dependent variable glycemia were evaluated by three-way ANOVA. Also, two-way ANOVA was used for each set of data for the diabetic and non-diabetic animals to check the influence of the factor treatment and time (fasting/overload) on glycemia. The Student-Newman-Keuls test was used to determine the differences among groups. The level of significance was set at $P < 0.05$.

Results

Experiment 1

The glucose tolerance test after each treatment showed that IMI and CNZ did not differ from CTR. In these 3 groups, fasting glycemia was about 60 mg/dl and there was an increase of blood glucose levels to more than 100 mg/dl at 30, 60, 90 and 120 min after glucose overload ($F(4,255) = 16.732$; $P < 0.001$).

No change in fasting glycemia was seen after *ip* administration of antidepressant drugs at doses already shown to induce behavioral effects. MOC, FLU and SER were different from the other treatments ($F(5,255) = 6.432$; $P < 0.001$) and there was an interaction be-

tween treatment and time of measurement ($F(20,255) = 2.455$; $P < 0.001$) (Figure 1). MOC significantly increased glycemia at 30 min and FLU increased glycemia at 90 and 120 min after glucose overload. The administration of SER induced a completely different glycemia pattern since it prevented

the expected increase in glycemia after glucose overload.

Experiment 2

The results of experiment 2 (Table 1) showed a significant difference between the

Figure 1 - Oral glucose tolerance test of non-diabetic rats treated with antidepressant agents. CTR: Vehicle, IMI: imipramine, MOC: moclobemide, CNZ: clonazepam, FLU: fluoxetine, SER: sertraline. Data are reported as means \pm SEM. * $P < 0.001$ compared to fasting; ** $P < 0.001$ compared to other times; + $P < 0.001$ compared to fasting; and 30 min; # $P < 0.001$ compared to other treatments (two-way ANOVA and Student-Newman-Keuls test).

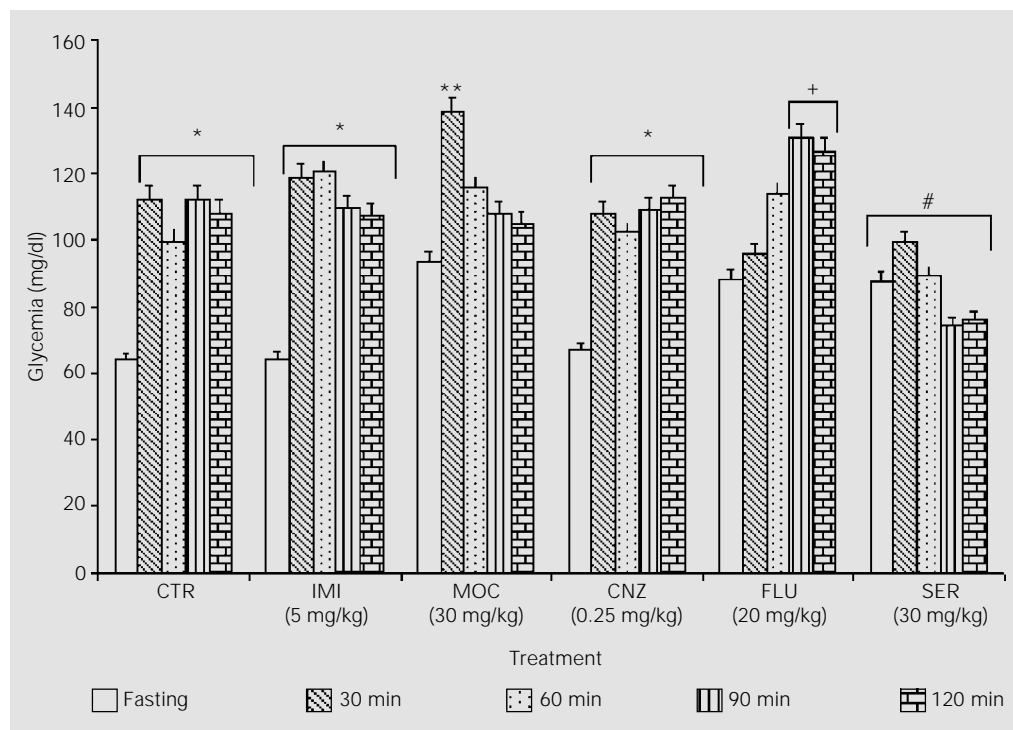


Table 1 - Fasting glycemia and glycemia measured 60 min after a glucose overload in diabetic and non-diabetic rats treated with different antidepressants.

Notice that diabetic animals present higher glycemia than non-diabetic animals. Data are reported as means \pm SEM. The number of animals is given in parentheses. * $P < 0.001$ compared to other treatments; + $P < 0.001$ compared to fasting (three-way ANOVA and Student-Newman-Keuls test).

	Treatment	Dose (mg/kg)	Non-diabetic (mg/dl)	Diabetic (mg/dl)
Fasting	Vehicle	-	70.3 \pm 3.5 (8)	364.1 \pm 43.9 (10)
	Imipramine	5	64.6 \pm 2.8 (9)	402.8 \pm 45.0 (7)
	Moclobemide	30	90.0 \pm 4.8 (10)	301.1 \pm 49.9 (10)
	Clonazepam	0.25	67.1 \pm 3.3 (9)	273.6 \pm 62.7 (7)
	Fluoxetine	20	89.1 \pm 5.3 (10)	313.2 \pm 53.9 (9)
	Sertraline	30	57.9 \pm 4.0 (9)	414.8 \pm 48.7 (9)
	Overload	Vehicle	-	96.7 \pm 3.4+ (8)
Imipramine		5	104.8 \pm 6.8+ (9)	507.3 \pm 15.8+ (7)
Moclobemide		30	110.9 \pm 5.5 (10)	380.2 \pm 37.5+ (10)
Clonazepam		0.25	125.5 \pm 8.6+ (9)	460.9 \pm 31.1+ (7)
Fluoxetine		20	158.3 \pm 14.3* (10)	404.9 \pm 55.0+ (9)
Sertraline		30	54.9 \pm 15.9* (9)	405.6 \pm 61.2+ (9)

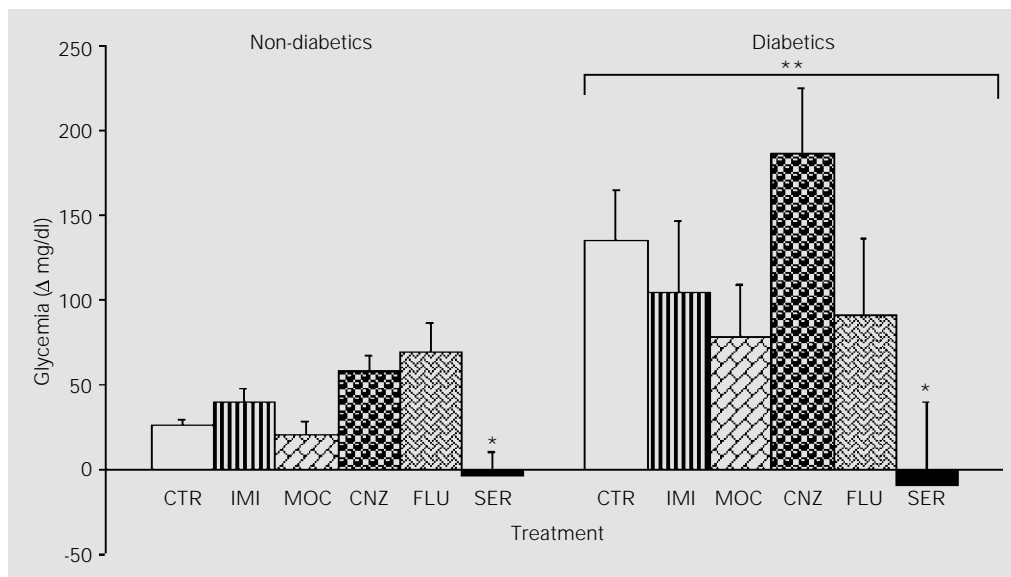


Figure 2 - Differences between glycemia measured during fasting and 60 min after the glucose overload. Diabetic and non-diabetic rats were treated with different antidepressants. CTR: Vehicle, IMI: imipramine, MOC: moclobemide, CNZ: clonazepam, FLU: fluoxetine, SER: sertraline. Data are reported as means \pm SEM. * $P < 0.001$ compared to other treatments; ** $P < 0.001$ compared to non-diabetics (two-way ANOVA and Student-Newman-Keuls test).

non-diabetic and the diabetic groups of rats ($F(1,186) = 480.12$; $P < 0.001$) and between fasting and overload condition ($F(1,186) = 23.29$; $P < 0.001$), and an interaction on non-diabetic/diabetic factor and treatment ($F(5,186) = 3.33$; $P = 0.007$).

Analysis of data from non-diabetic animals showed a significant difference between fasting and overload ($F(1,96) = 56.86$; $P < 0.001$). Antidepressant treatment modified glycemia ($F(5,96) = 15.94$; $P < 0.001$) and an interaction was observed ($F(5,96) = 5.52$; $P < 0.001$). As seen in experiment 1, groups treated with vehicle, IMI, CNZ and FLU presented higher 60-min overload glycemia compared to the fasting condition. For the groups treated with MOC or SER no difference was observed between fasting and overload glycemia. FLU significantly increased overload glycemia and SER significantly decreased it when compared to overload glycemia plus vehicle. None of the treatments changed fasting glycemia values in non-diabetic rats.

Considering the differences between overload and fasting glycemia, a significantly higher delta value was detected for diabetic animals ($F(1,94) = 15.247$; $P < 0.001$) and treatment with SER prevented the increase

of blood glucose levels after overload both in diabetic and non-diabetic rats ($F(5,94) = 4.398$; $P = 0.001$) (Figure 2).

Discussion

Our results demonstrate that different groups of antidepressant drugs cause diverse changes in glycemia in diabetic and non-diabetic rats, mostly after glucose overload. The most important changes in glycemia in non-diabetic rats occurred after the administration of FLU, which caused an increase in glycemia during the post-oral glucose phase of the test. The maintenance of blood glucose levels during the overload test induced by SER was impressive both in non-diabetic and diabetic animals and showed that SER has a different action profile compared to the other treatments. Interestingly, SER did not cause hypoglycemia with the antidepressive dose tested.

Depression treatment in diabetes is important because it improves the quality of life, increases treatment compliance, and permits patients to achieve better glycemia control, which may reduce long-term complications and emergencies. Depending on depression intensity, pharmacological intervention is obligatory. Antidepressants might

also be used as a prophylactic treatment for diabetic patients (7,11,17). Therefore, the effects on blood glucose control caused by antidepressant drugs and their interaction with oral hypoglycemic agents or insulin need to be known. As was observed in several other studies, the classical antidepressant (23) and monoamine oxidase (MAO) inhibitors most frequently induce hyperglycemia (18,24) in patients and other animal species (19,25). In the clinical setting, adjustment of doses of hypoglycemic agents might be necessary (26-29). In the present study, the changes in glycemia induced by MOC, a MAO inhibitor, were found to be ephemeral, occurring only immediately after MOC administration.

A very effective and frequently used antidepressant class is that of selective serotonin reuptake inhibitors (30), considered to have few adverse effects (18). However, it is recognized that fluoxetine increases insulin receptor sensitivity (31) and competes with sulfonylurea for cytochrome P-450 metabolism (29), requiring adjustment of the doses of insulin or hypoglycemic agents to avoid hypoglycemia (32,33). On the other hand, non-insulin-dependent diabetic patients who are treated with fluoxetine show a consistent reduction in carbohydrate consumption and weight loss associated with a decrease in HbA1c (34,35). Ultimately, sertraline may be a better agent for depression treatment in diabetic patients (36). In this preclinical study, fluoxetine induced peaks of increased glycemia while sertraline prevented the increase in glycemia after glucose overload. Further studies are needed to determine whether this acute effect will be still demonstrable after long-term treatment, as seen in mice (19). The explanation for the effect seen after sertraline may be associated with an increase in plasma insulin concentration after glucose overload in streptozotocin-induced diabetic and non-diabetic rats, as evidenced in a preliminary study undertaken in our laboratory. However, a reduction in intestinal glu-

cose absorption or an increase in peripheral insulin receptor sensitivity cannot be ruled out and needs further study. Despite the antidepressant group classification based upon their mechanisms of action, several differences in specificity occur among the agents. Fluoxetine and sertraline are selective serotonin reuptake inhibitors, but sertraline is a more powerful serotonin and dopamine reuptake inhibitor than fluoxetine, while fluoxetine is more potent as an antagonist of 5-HT₂ receptors (37). It is still necessary to clarify whether the neurochemical differences are responsible for the differences in effects seen in the present study.

Other neurotransmitter systems might participate in depression (38). Alprazolam has been demonstrated to be effective as an antidepressant (5,39). In preclinical studies, clonazepam has shown an antidepressant effect in streptozotocin-induced diabetic rats (21). Diazepam, another benzodiazepine agent, increases fasting glycemia and decreases glucose overload glycemia in diabetic rats (40). Thus, there is interest in the present demonstration that clonazepam does not change the fasting and overload glycemic levels in diabetic and non-diabetic rats, confirming that this agent is a good alternative for the treatment of depression in diabetics.

Depression in diabetic patients must be treated or prevented by first using simple and non-pharmacological interventions for improving quality of life. When antidepressants are deemed necessary, sertraline seems to be a good first choice agent (36) due to its well-documented stabilization of glucose levels. As a second choice to avoid disturbances in glycemia, clonazepam seems to be a safe antidepressant drug for diabetics.

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