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ORIGINAL STUDY

Effect of Selective Serotonin Reuptake Inhibitors on Blood Glucose in Euglycemic and Streptozotocin-induced Diabetic Albino Wistar Rats

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Abstract

Background: **Diabetes mellitus is one of the serious health concerns around the globe, characterized by hyperglycemia. It is also linked with several other disorders including neuropathy. One of the most typical diabetes-related comorbidities is depression.**

Objectives: **In this investigation, euglycemic albino rats and streptozotocin-induced diabetic albino Wistar rats were used to assess the effects of fluoxetine, escitalopram, and fluvoxamine on blood glucose levels.**

Method: **To measure euglycemic index, the three medications were given to several groups. After administering glucose, the blood glucose level was checked at 0, 60, and 150 min. Additionally, starting on the third day following the induction of diabetes, the test medications were given for a total of 28 days. The CBG (Capillary blood glucose) levels were assessed on days 0, 7, 14, 21, and 28.**

Results: **According to the study, fluoxetine, escitalopram, and fluvoxamine have a hyperglycemic effect because the CBG values were significantly higher ($p < 0.05$) in the test groups at all time points in both euglycemic albino Wistar rats after glucose challenge and in rats with diabetes mellitus caused by streptozotocin.**

Conclusion: **Based on the findings it can be suggested that the three anti-depressant drugs also possess hyperglycemic effects. The percentage of increase of CBG level was maximum with fluoxetine followed by fluvoxamine group and less with escitalopram at the all-time interval of OGTT. This indicates that the tendency of induction of hyperglycemia due to glucose challenge was more with fluoxetine & and fluvoxamine compared to escitalopram which may depict the relative safety of escitalopram as compared to fluoxetine & fluvoxamine as antidepressants in diabetic conditions. To ascertain this, further studies need to be performed to assess the mechanism of action of the drugs in bringing about hyperglycemic effects.**

Keywords: Anti-depressant, Hyperglycemic, Fluoxetine, Escitalopram, Fluvoxamine, CBG, OGTT and SSRI

1. Introduction

The leading endocrine illness in the world, diabetes mellitus, results in a disrupted metabolism and is typically brought on by a combination of genetic and environmental factors [1]. Hyperglycemia is a complication characteristic to diabetes that is caused by impaired insulin secretion, poor glucose utilisation, or increased glucose synthesis [2]. According to the International Diabetes Federation, there will be 380 million diabetics globally by 2025, up from 240 million in 2007 [3]. There were 19 million diabetic patients in India in 1995; by 2030, there will be 643 million, and by 2045, there will be 783 million [4]. As a result, India will be

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the world's diabetes capital, signalling that the worldwide population is on the verge of a diabetes pandemic.

Uncontrolled hepatic glucose output, decreased glucose absorption by skeletal muscle, adipose tissues, and other peripheral tissues, as well as impaired glycogen synthesis, are the main causes of hyperglycemia [5,6]. When the renal glucose reabsorption threshold is exceeded, glucose occurs in urine owing to osmotic diuresis (polyuria), resulting in dehydration, thirst, and increased water consumption (polydipsia). Insulin insufficiency promotes skeletal muscle atrophy by deregulating the protein homeostasis [7]. Because the pancreatic beta cells regulate the glucose homeostasis by increasing insulin release, glucose tolerance stays near-normal in the early stages of the disease despite insulin resistance. The pancreatic islets become unable to maintain the hyperinsulinemic situation when insulin resistance and compensatory hyperinsulinemia progress in some patients [8]. Impaired glucose tolerance, defined by postprandial glucose overload follows. A reduction in insulin secretion and an increase in the synthesis of hepatic glucose are the two main factors that lead to overt diabetes [9].

Diabetes is associated with several complications that arise due to a persistent circulating glucose. It has two immediate complications: hyperglycemic hyperosmolar state (HHS) and diabetic ketoacidosis (DKA) [10]. DKA is brought on by an excess of a counter-regulatory hormone (glucagon, catecholamines, cortisol, and growth hormone) and an insulin deficiency, either absolute or relative (glucagon, catecholamines, cortisol, and growth hormone). Furthermore, chronic hyperglycemia causes a variety of consequences including chronic renal failure, which is a large and quickly growing problem [11,12]. Type II diabetes mellitus is currently one of the most difficult health-care issues, requiring optimal management. This metabolic disorder is treated with insulin, sulfonylureas, biguanides, -glucosidase inhibitors, and DPP-4 inhibitors [13].

Glycemic index is a number from zero to hundred, which represents the relative rise in glucose level 2 h post consumption of food. The incremental area under the 2-h blood glucose response curve (AUC) following a 12-h fast and consumption of a food containing a specific amount of accessible carbohydrate (often 50 g) is referred to as the glycemic index of a food. The AUC of the test meal is multiplied by 100 and divided by the AUC of the standard, which can be either glucose or white bread, providing two alternative definitions. Based on information gathered from 10 human individuals, the average GI value is determined. There must be an equivalent amount of accessible carbohydrates in the standard and test foods. Each of the evaluated foods receives a relative rating as a consequence [14].

List of abbreviations

AUC	Area under the curve
ATP	Adenosine Triphosphate
ANOVA	Analysis of Variance
CBG	Capillary Blood Glucose
DKA	Diabetic Ketoacidosis
HHS	hyperglycemic hyperosmolar state
DPP-4	Dipeptidyl peptidase − 4
GLUT-2	Glucose transporter − 2
SSRI	Selective Serotonin reuptake receptors
SNRI	serotonin noradrenaline reuptake inhibitors
MAOIs	Monoamine Oxidase inhibitors
TCAs	Tricyclic anti-depressants
SERT	Serotonin transporters
5-HT	5-Hydroxytryptamine
OGTT	Oral Glucose Tolerance Test
OHG	Oral hypoglycaemics

Insulin is a hypoglycemic hormone released by the human pancreas once glucose enters the cell via GLUT-2 [15]. Increased glucose causes the ATP-sensitive K^+ channel to be inhibited, resulting in cell depolarization. It increases the amount of Ca^{++} that enters cells through voltage-sensitive L type calcium channels and the amount of Ca^{++} that is released from intracellular binding sites like the mitochondria, sarcoplasmic reticulum, and the internal surface of the cell membrane. This causes the release of insulin through the degranulation of stored vesicles [16].

Depression and diabetes are closely associated with each other. Depression has been associated with behaviours like smoking, lethargy, and increased calorie intake. They collectively raise the danger of type 2 diabetes [17]. It has been linked to central obesity as well as poor glucose tolerance in some cases. Furthermore, there is a strong link between depression and physiological abnormalities including hypothalamic−pituitary−adrenal axis activation, the sympathoadrenal system, and proinflammatory cytokines, all of which can increase the risk of developing insulin resistance and diabetes [18]. Patients with type 2 diabetes have lower amounts of the body's autoregulatory systems, including neurotransmitters like noradrenaline, dopamine, and serotonin, which raises the risk of depression. Depression is three times more prevailing in diabetic patients than in those who do not have the disease [6,19]. Diabetic patients have a more severe mental disorder, a longer treatment

period, and a higher rate of relapse. Diabetes mellitus is frequent in patients who have previously been diagnosed with depression, and diabetics may experience depression as a side effect of treatment. With the onset of depression, diabetic sequelae such as macroangiopathy, retinopathy, and polyneuropathy ensue [20,21].

Type 2 diabetes seems to cause depression at an early stage. According to data, depression in people without diabetes is independently linked to a 37−60% higher future risk of getting type 2 diabetes [22]. The occurrence of these disorders together may be the cause of diabetes worsening. Psychotherapy or its combination with medication is frequently used to treat depression. Selective serotonin reuptake inhibitors (SSRIs) are the drugs of preference for the treatment of depression [23,24]. There are several medications on the market right now that can be used to treat depression, which includes reversible inhibitors of monoamine oxidase such as clorgeline, serotonin noradrenaline reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine, SSRI such as escitalopram, fluvoxamine, and atypical antidepressant such as trazodone and mianserin [25].

Antidepressant safety and tolerability have improved significantly since the advent of SSRIs, which have little or no affinity for cholinergic, adrenergic, or histamine receptors and do not cause hindrance to cardiac conduction. Patients with heart disease and the elderly can handle tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) without any problems, who are particularly susceptible to the anticholinergic and orthostatic effects of these drugs [26,27]. The strong selectivity of SSRIs for the nerve terminal serotonin reuptake system has reinforced the theory that these drugs exert their therapeutic effects by modulating serotonin neurotransmission in the brain. Many medications used to treat a variety of disorders, interact with receptors involved in the release of insulin, resulting in hypo- or hyperglycemia [12,28]. So, it makes sense to assess them considering this. It is expected that SSRIs influence glucose metabolism. It could be hypothesised that SSRIs inhibit membrane associated serotonin transporter (SERT), leading to decreased intracellular serotonin levels in beta cells and hence decreased insulin release, more so during glucose challenge. Simultaneously, SSRIs increases extracellular serotonin available for binding with 5HT receptors (5-Hydroxytryptamine receptors) such as 5HT2c and 5HT1A, found in pancreatic beta cells. 5-HT receptors are groups of G-protein coupled receptors ligand gated ion channels found in central and peripheral nervous system. These receptors mediate both excitatory and inhibitory neurotransmitters. These receptors influence various biological and neurological processes such as sleep, anxiety, appetite, memory, and learning. When these receptors are activated, it leads to inhibition of insulin release. Expression of 5HT1a and 5HT3c trigger adrenal catecholamine release and cause hyperglycemia. By the above-mentioned mechanisms, it could be hypothesized that SSRIs causes hyperglycemia. Therefore, the objective of the current study is to investigate the impact of SSRIs (fluoxetine, escitalopram, fluvoxamine) on blood glucose levels in diabetic rat models and euglycemic albino rat models after the induction by streptozotocin.

2. Materials and methods

2.1. Reagents preparation

Streptozotocin: 500 mg of streptozotocin was dissolved in 25 ml of sodium citrate buffer (0.1 M, pH 4.5) and given intraperitoneally in the dose of 55 mg/kg BW. **Glibencamide:** 0.5 mg/kg BW of glibencamide was dissolved in 2.0 ml of 1% gum acacia solution, resulting in a concentration of 0.25 mg/mL. Six rats received 0.5ml/rat orally each day. A daily oral dose of 4.5 mg/kg body weight of fluoxetine, suspended in 1% gum acacia, was given to 12 rats. **Escitalopram:** 1.8 mg/kg body weight (suspended in 1% gum acacia) was administered orally every day to 12 rats. **Fluvoxamine:** 18 mg/kg body weight (suspended in 1% gum acacia) was administered orally every day to 12 rats.

2.2. Animals

Wistar strain adult healthy albino rats weighing 150−250g of either sex were used. The rats were inbred in the Department of Pharmacology's central animal house at J.S.S Medical College in Mysore, under ideal housing, temperature, ventilation, and nutrition conditions. The animals had unrestricted access to commercial laboratory food and water. They were maintained at a constant temperature of 24 ± 2 °C, a relative humidity range of 30−70%, and a 12-h light−dark cycle. The JSS Medical College in Mysore's institutional ethical committee gave its approval (JSSMC/IAEC/03/August 2017 dt. 23/07/2017). Healthy animals weighing 150−250 gms with an age group of 3−4 months were considered for the study, whereas, animals weighing more than 250 gms and less than 150 gms, age <3 months and >4 months and pregnant and lactating females were not considered. The experiment was split into two

sections. The first section involved tests on euglycemic rats, while the second half involved developing diabetes using streptozotocin and monitoring CBG levels after the test medicines were administered. Based on the above-mentioned criteria, animals were grouped for euglycemic index (Table 1) and treatments were given (Table 2).

2.3. Induction of diabetes

In the study, 30 rats were intraperitoneally injected with newly manufactured streptozotocin (dissolved in sodium citrate buffer) at a dose of 55 mg/kg body weight in an aseptic setting 3 days before the experiment, following an overnight fast. For the first 24 h after the injection, the animals were closely monitored for any signs of allergic responses, behavioural abnormalities, seizures, or hypoglycemia crises. There were no unfavourable effects in any of the animals. Blood sugar levels were assessed every morning at 9:00 a.m. for three days. After three days, the animals developed stable hyperglycemia. For the experiment, only animals with blood glucose levels greater than 250 mg/dL were used.

2.4. Estimation of blood glucose

Fasting blood glucose was determined using an Accucheck glucometer on days 0, 1, 3, 7, 14, 21, and 28 after blood was drawn from 12-h-starved rats using the rat tail puncture procedure 1 h after the administration of each dose of the various medications.

Table 1. Animals grouping for euglycemic index.

Group	Treatment details for euglycemic index
Group 1	Control rats received 0.5 ml 1% gum acacia (oral).
Group 2	4.5 mg/kg of body weight in fluoxetine was administered orally
Group 3	1.8 mg/kg of escitalopram (oral)
Group 4	fluvoxamine 18 mg/kg body weight(oral).

2.5. Statistical analysis

A statistical analysis was done on the data from the current investigation. The mean and standard deviations for each group were computed. A one-way ANOVA was used for multiple group comparisons, and the statistical significance of differences between groups was assessed using a post hoc Tukey's test. p values under 0.05 were considered significant.

3. Results

3.1. Evaluation of euglycemic index

In comparison to the control group, the fluoxetine, fluvoxamine, and escitalopram groups all displayed an increase in CBG levels, with the highest increase occurring at the 60-min mark. In this regard, the increase was more prominent in the case of fluoxetine treated groups compared to escitalopram and fluvoxamine treated groups (Table 3). Thus, the increase in CBG levels of the three groups were statistically significant ($p < 0.05$) at 0 min, 60 min and 150 min. The percentage increase of CBG level was almost equal in fluoxetine and fluvoxamine group and was considerably more compared to escitalopram at 0 min. It was considerably more with fluoxetine compared to fluvoxamine & escitalopram at 60 min and 150 min. Escitalopram and fluoxetine considerably raise capillary blood glucose levels as compared to control, but fluvoxamine and the control have nearly identical levels at 0–60 min. At 60–150 min it was almost the same for control, escitalopram & fluvoxamine but increased for fluoxetine. When compared to control, it was higher

Table 2. Animals grouping for the diabetic rats.

Group number	Treatment details
Group 1	**Normal Control Group:** 0.5 ml of oral, 1% gum acacia from 0 to 28 days, normal rats in a euglycemic state received daily oral administration of 1% 0.5 ml gum acacia.
Group 2	**Diabetic Control:** 0.5 ml of oral 1% gum acacia from 0 to 28 days, diabetic rats received 0.5 ml of 1% gum acacia orally.
Group 3	**Standard 0.5 mg/kg BW glibencamide (oral):** Diabetic rats were treated with 0.5 mg/kg BW glibencamide orally from 0 to 28 days.
Group 4	**Test 1:** 4.5 mg/kg BW fluoxetine (oral) Diabetic rats were treated with 4.5 mg/kg BW fluoxetine suspended in gum acacia orally from 0 to 28 days.
Group 5	**Test 2:** 1.8 mg/kg BW escitalopram(oral) Diabetic rats were treated with 1.8 mg/kg BW escitalopram suspended in gum acacia orally from 0 to 28 days.
Group 6	**Test 3:** 18 mg/kg BW fluvoxamine (oral) Diabetic rats were treated with 18 mg/kg BW fluvoxamine suspended in gum acacia orally from 0 to 28 days.

Table 3. -Capillary Blood glucose (CBG) levels in control, escitalopram, fluvoxamine, fluoxetine groups and the difference between the control, escitalopram, fluvoxamine, fluoxetine groups equivalent intervals of time.

	Capillary Blood glucose concentration in mg/dL						
Time interval during OGTT	Control group (N = 6)	Escitalopram group (N = 6)	fluvoxamine group (N = 6)	Fluoxetine group (N = 6)	Rise in CBG levels escitalopram group relative to the control group	Rise in CBG levels fluvoxamine group compared to control group	Rise in CBG levels fluoxetine group compared to control group
0 min	64.66 ± 2.73	74.66 ± 2.16	92.33 ± 2.58	92.5 ± 1.87	10 ± 0.57 *	28.33 ± 0.15**	**28.16 ± 0.86****
60 min	89.83 ± 2.48	107.66 ± 3.01	113 ± 3.03	127.5 ± 1.87	17.83 ± 0.53**	23.17 ± 0.55**	37.67 ± 0.61**
150 min	78 ± 2.09	92.16 ± 3.06	102.33 ± 2.25	110.33 ± 4.27	14.16 ± 0.97 *	24.33 ± 0.16**	32.33 ± 2.16**

Data is expressed as mean ± SD of (n = 6), *p < 0.05 and * *p < 0.01 compared with control (distilled water).

for escitalopram and fluoxetine but almost the same for fluvoxamine at 0−150 min.

3.2. Effect of fluoxetine, escitalopram, fluvoxamine on streptozotocin induced diabetic albino wistar rats

While the control rats displayed little to no change in blood glucose levels, the diabetic control rats displayed rising hyperglycemia (**Table 4**). The test medications, escitalopram, fluvoxamine, and fluoxetine, demonstrated a minor increase in blood glucose levels from D0 to D3, but then a continual increase up to D28. In contrast, the conventional treatment showed a sustained decline in blood glucose levels from D0 to D28. By contrasting the standard and test groups with the diabetic control group, the percentage change in blood glucose levels in each group was also computed. There was a progressive decrease in the CBG level in the standard group. The percentage increased from D3 to D7 in case of escitalopram group and then there was a gradual decrease in the CBG levels to reach almost initial reading by D28. Percentage CBG levels in the fluvoxamine group showed a gradual decrease from D0 to D28. The percentage of CBG levels between D3 and D28 in the fluoxetine group did not differ significantly from one another.

Furthermore, percentage change in blood glucose value of standard and test groups was calculated by comparing with that of the diabetic control group. There was a progressive decrease in CBG level in the standard group. However, the percentage of CBG levels increased from D3 to D7 in case of escitalopram group followed by a gradual decrease in CBG levels to reach almost initial reading by D28. Similarly, the CBG levels in the fluvoxamine group showed a gradual decrease from D0 to D28. Conversely, there was no discernible change between the proportion of CBG levels at D3 and D28 in the fluoxetine group.

4. Discussion

Chronic metabolic disease Type 2 Diabetes Mellitus has a significant impact on people's health, quality of life, and life expectancy as well as the healthcare system [29,30]. Exercise, diet, and weight loss are the most effective and important ways to regulate high blood glucose levels, and they are regarded as the most important ways to improve glucose homeostasis [30]. However, management of this condition by lifestyle changes alone is insufficient, or patient compliance may be difficult, leaving the option of conventional drug therapies such as

Table 4. Effect of fluoxetine, escitalopram, fluvoxamine on blood glucose levels in streptozotocin-induced diabetic rats.

	Groups	D0	D3	D7	D14	D21	D28	Difference between CBG levels of D0& D28
1	Control	80.5 ± 4.50	80.33 ± 4.96	82 ± 6.78	81.83 ± 4.75	79.5 ± 5.61	79.83 ± 4.57	−0.67
2	Diabetic control	351.16 ± 11.80	382.16 ± 20.15	389.33 ± 23.82	405.5 ± 22.79	420.66 ± 23.76	438.83 ± 25.76	87.67
3	Standard	358.8 ± 15.94	327.33 ± 17.52	301.33 ± 19.07	265.5 ± 22.75	200.16 ± 24.70	173.66 ± 24.48	−185.14
4	Escitalopram	360.33 ± 12.53	444.33 ± 3.50	477.33 ± 6.56	484.5 ± 6.78	492.67 ± 9.63	501.17 ± 7.1	140.84
5	Fluvoxamine	355.33 ± 18.69	476.83 ± 8.84	483 ± 9.09	488.5 ± 4.64	496.33 ± 5.65	511.33 ± 4.68	156
6	Fluoxetine	358.33 ± 16.47	407.33 ± 6.89	407 ± 7.35	444.33 ± 11.02	454.83 ± 4.62	468.17 ± 4.54	109.84
	GR.1(CONTROL) V/S GR.2,3,4,5 AND 6	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	

D 0 = before giving the drug but after induction of diabetes with streptozotocin, D1 = Day 1 of test drugs/standard, D 3, D 7, D 14, D 21, D 28 = 3rd, 7th, 14th, 21st, 28th days of administration of the drugs, respectively.

sulfonylureas, biguanides, α-glucosidase inhibitors, in many patients, thiazolidinediones, incretin mimics, and insulin are used either separately or in conjunction with oral hypoglycemic medications [21,31].

One of the most prevalent comorbidities of Type 2 diabetes in this regard is depression. Currently, the preferred medications for treating depression are selective serotonin reuptake inhibitors (SSRI) [32,33]. Hence an earnest attempt is made in this research to determine the impact of SSRIs fluoxetine, escitalopram, and fluvoxamine on glycemic levels in euglycemic albino wistar rats after glucose challenge and streptozotocin induced diabetes mellitus in albino wistar rats since serotonin acts as a regulator of insulin secretion which is co-localized with insulin in granules of pancreatic β-cells [33,34].

In the present study, the basal levels of CBG at 0 min in OGT test were high in the test groups, i.e., 92.5 mg% in fluoxetine and 92.33 mg% in fluvoxamine whereas 74.66 mg% in escitalopram compared to basal levels of CBG of control was 64.66 mg% which indicates hyperglycemic effect of SSRIs even before glucose challenge probably related to its effect on basal insulin secretion. This effect was more with fluoxetine & fluvoxamine whereas less with escitalopram [34,35].

At 60 min, CBG levels again increased in comparison with that of the 0 min reading with an average of 107.66 mg% in escitalopram group, 113 mg% in fluvoxamine group and 127.5 mg% in fluoxetine group which were significantly higher than the corresponding control CBG levels which averaged to 89.83 mg%.

At 150 min, CBG reading was 92.16 mg% in the escitalopram treated group 102.33 mg% in fluvoxamine group 110.33 mg% in fluoxetine treated group. This CBG reading of test drugs treated groups was significantly higher than the corresponding control readings which was 78 mg% which indicate sustained hyperglycemic effect of SSRI even after the effect of glucose challenge. This is probably related to longer half-life of SSRIs used in this study.

At all-time intervals, the fluoxetine group demonstrated an increase in CBG levels compared to the control, with the greatest increase at 60 min (optimal glucose challenge effect time) the increase was more with Fluoxetine compared to Escitalopram & fluvoxamine which indirectly indicate that SSRIs can blunt the glucose induced insulin secretion [36,37]. This can be explained based on increased basal glucose levels and effect of glucose challenge in releasing insulin from the beta cells.

The percentage of increase of CBG level was maximum with fluoxetine followed by fluvoxamine group and less with escitalopram at the all-time interval of OGTT. This indicates that tendency of induction of hyperglycemia due to glucose challenge was more with fluoxetine & fluvoxamine compared to escitalopram which may depict relative safety of escitalopram as compared to fluoxetine & fluvoxamine as antidepressants in diabetic condition.

The Capillary blood glucose levels of escitalopram, fluvoxamine and fluvoxamine was higher The CBG level inter interval differences at all time intervals, including 0–60 min, 60–150 min, and 0–150 min, are significantly larger when compared to control and were statistically significant ($p < 0.05$) [37,38]. According to the theory, SSRIs have a significant effect on basal blood glucose levels after a glucose challenge in albino wistar rats that are euglycemic as well as a notable hyperglycemic effect in albino wistar rats that have streptozotocin-induced diabetes mellitus when compared to the diabetic control group at all time intervals [39,40]. Because of the above demonstrated hyperglycaemic effect of escitalopram, fluvoxamine, and fluoxetine in animals, it is possible that they can worsen glucose-induced glycemic changes and may be involved in beta cell destruction [41]. It is possible that they can worsen glycaemic control in well controlled, uncontrolled diabetes mellitus, prediabetics, high risk diabetics (decreased basal & glucose induced insulin secretion) and may be even in normoglycemic individuals (decrease basal insulin secretion) in human subjects also and additional research is needed to support the same [42,43].

5. Conclusion

Depression is a significant co-morbidity of Type 2 diabetes. Till date, the most preferred medicine to treat depression are SSRIs (selective serotonin reuptake inhibitors). Because SSRIs block the membrane-associated serotonin transporter (SERT), beta cells produce less insulin when faced with a glucose challenge because there is less intracellular serotonin in the cells. The availability of extracellular serotonin for binding with 5HT receptors, such as 5HT2c and 5HT1A, located in pancreatic beta cells, is simultaneously increased by SSRIs. The activation of these receptors inhibits the release of insulin. Additionally, 5HT1a and 5HT3c expression lead to hyperglycemia and adrenal catecholamine release. Therefore, the goal of the current study is to determine how SSRIs (fluoxetine, escitalopram, and fluvoxamine) affect blood glucose levels in diabetic rat models and euglycemic albino rat models after the induction by streptozotocin. Initially, the CBG levels were measured using the three anti-depressant drugs at 0 min, 60 min and 150 min. Further, the effects of three anti-depressant drugs on blood glucose was studied using Streptozotocin induced diabetic rats for 28 days. The fluoxetine group showed higher CBG levels than the control group at all time points, with the highest increase occurring at 60 min (the ideal period for the impact of a glucose challenge), with the fluoxetine group's increase being greater than that of escitalopram and fluvoxamine. Considering the findings of the current study, it can be concluded that escitalopram, fluvoxamine, and fluoxetine may mitigate the effects of concurrently administered OHGs during the management of type 2 diabetes mellitus, but escitalopram may demonstrate relative safety of escitalopram as compared to fluoxetine & fluvoxamine as antidepressants in diabetic condition. In addition, using these drugs with OHGs may need dose escalation of the OHGs to compensate for the glycemic worsening effect caused by SSRIs by the inhibition of insulin secretion as put forth in the hypothesis at the beginning. Further, a detailed study is required to study the mechanism of action of the drugs in bringing about hyperglycemic effects.

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Ethical approval for animal studies

The JSS Medical College in Mysore's institutional ethical committee gave its approval (JSSMC/IAEC/03/August 2017 dt. 23/07/2017).

Conflict of interest

The authors declare that there is no conflict of interest.

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