Effect of Selective Serotonin Reuptake Inhibitor Sertraline on Hormonal Regulation of Blood Glucose in Normal and Diabetic Male Albino Rats

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ABSTRACT

The present work was done to investigate the effect of selective serotonin reuptake inhibitor sertraline on the hormonal regulation of blood glucose in normal and diabetic male albino rats. This work was carried out on 36 male albino rats. The rats were weighed and divided into two groups, A-Normal group: subdivided into three subgroups: Group (1): is the control group, group (2): treated by oral administration of sertraline in a dose of 30mg/kg/day through intragastric tube for one week, group(3): treated by oral sertraline in a dose of 30mg/kg/day through intragastric tube for three weeks. B-Diabetic group: diabetes was induced by single injection of 50mg/kg streptozotocin intraperitonealy to all rats, then rats subdivided into 3 subgroups. Group(1): is the control diabetic group, group (2): diabetic rats treated by oral administration of sertraline 30mg/kg/day through intragastric tube for one week, group(3): diabetic rats treated by oral administration of sertraline 30mg/kg/day through intragastric tube for three weeks. At the end of the experiment, rat were fasted for night, weighed, scarified, and blood samples were collected for determination of glucose, catecholamines, glucagon, ACTH, corticosterone and insulin levels. The results showed significant reduction of blood glucose in normal and diabetic groups after one and three weeks of treatment by sertraline. Epinephrine was significantly increased after one and three weeks of treatment in normal and diabetic groups. Norepinephrine and glucagon were significantly increased after three weeks treatment by sertraline in normal and diabetic groups. Non significant change of insulin, ACTH, corticosterone and body weight in normal and diabetic groups. It is concluded that sertraline treatment induced hypoglycemia and stimulated adrenomedullary response. It is recommended to use sertraline in diabetic patients, and to reduce the dose of antidiabetic drugs during sertraline treatment.

INTRODUCTION

Patients with diabetes exhibit higher rate of depression compared to other peoples[(1)]. Comorbid diabetes and depression are associated with hyperglycemia and poor glycemic control[(2)], with an accelerated progression of complication associated with diabetes[(3)], and increased risk of mortality [(4)].

Selective serotonin reuptake inhibitors(SSRIs) are the drugs of choice for the treatment of depression, and the majority of clinical studies support their use in diabetes and

depression[5]. Diabetic patients treated by SSRIs can exhibit reduced fasting glucose levels, reduced body weight and improved glycemic control compared with diabetic patients using other antidepressants. Also, selective serotonin reuptake inhibitors thereby effectively reduces depression and prevents its recurrence in diabetic patients[5]. Similar to other antidepressant, SSRLs can impact blood glucose level particularly in diabetic patients, with an increase in the frequency and severity of hypoglycemia with absence of hypoglycemic symptoms[7]. Hypoglycemia associated with SSRIs thereby may be particularly a problem for intensively managed type 1 and type 2 diabetic patients. Intensive insulin or glucose lowering therapies aimed at maintaining tight glycemic control are associated with a three-to four fold increase in the incidence of sever hypoglycemia with SSRIs treatment[8]. As a result of recurrent hypoglycemia, the hormonal counterreglulatory responses normally elicited by decrease of plasma glucose become impaired, thus increasing the risk for future bouts of hypoglycemia[9]. Impaired hypoglycemic counterregulation is a component of the clinical syndrome of hypoglycemia-associated with autonomic failure[9]. Serotonergic mechanisms have long been known to modulate neuroendocrinal responses, which are critical to hypoglycemia counterregulation. The association between SSRIs and hypoglycemia may be due to SSRIs-induced impairment of counterregulation mechanisms. Treatment with SSRIs in humans suppresses basal sympathetic nervous system activity[10]. Also serotonin neurons located in the caudal hindbrain are directly sensitive to changes in glucose availability[11]. Therefore, SSRIs may reduce the sensitivity of glucose sensing neurons that contributes to the activation of hormonal counterreglulatory responses.[11]

The aim of the present work was to study the effect of SSRIs sertraline, on blood glucose regulation, autonomic and neuroendocrinal responses in adult normal and diabetic male albino rats.

MATERIALS & METHODS

36 adult male albino rats weighing from 230-275gm were housed individually at room temperature with maintained dark light schedule (12am: 12pm hours). Rats were fed milk and bread and has free water access: The rats were divided into two groups.

A- Normal group: contained 18 rats subdivided into three equal subgroups each containing 6 rats:
Group (1): The normal control rats were administrated 1/2 ml oral saline through small intragastric tube.
Group (2): Rats were treated by oral sertraline(Apex Pharma) through small intragstric tube in a dose of 30mg/kg/day [12] for one week.
Groups (3): Rats were treated by oral sertraline through small intragastric tube in a dose of 30mg/day for three weeks.

B- Diabetic group contained 18 rats. Diabetes was induced by single intraperitoneal injection of

streptozotocin 50mg/kg (13). The rats were subdivided into three equal groups each containing 6 rats.

Group (1): The control diabetic group, rats were administrated 1/2 ml oral saline through small intragastric tube.

Group (2): Diabetic group treated by oral administration of sertraline in a dose of 30mg/kg/day for one week.

Groups (3): Diabetic group treated by oral administration of sertraline in a dose of 30mg/kg/day for three weeks.

At the end of the experimental period, rats were fasted for night, weighed, scarified and blood samples were collected and serum and plasma were separated for determination of:

Serum glucose level: according to the method of Tietz[14].

Glucagon level: according to the method of Evans et al, [15].

Corticosterone level: according to the method of Rasmussen et al., [16]

Epinephrine and nor-epinephrine levels: according to the method of Evans et al.,[17].

Adrenocorticotrophic hormone (ACTH) level: according to the method of Wilkinson and Raff [18].

Insulin according to the method of Burrin [19].

Statistical analysis

Results were tabulated as mean values ± DS, and analysis was performed. Comparison between studied groups were performed with independent samples student t-test. Analysis of variance was calculated, P values of <0.05 were considered statistically significant.

RESULTS

The results of the present work are shown in table (1):

Serum glucose level:

Sertraline treatment for one week showed, significant reduction of blood glucose level in normal and diabetic rats compared with the control, P< 0.05. Also, there was significant reduction of blood glucose level in normal and diabetic groups treated by sertraline for three weeks compared with the control, (P<0.05), Fig (1).

Epinephrine level:

The results showed significant increase in levels of epinephrine both normal and diabetic rats, after one or three weeks sertraline treatment compared with control, P<0.05, (Fig (2)

Norepinephrine level:

The results showed non significant change in norepinephrine level after one week of sertraline treatment in normal and diabetic rats. There was significant increase of norepinephrine level after three weeks of sertraline treatment in normal and diabetic groups compared with the control, p<0.05, Fig (3)

Glucagon level:

The results showed non significant change in glucagon level after one week of sertraline treatment in normal and diabetic groups. Normal and diabetic groups treated by sertraline for three weeks showed significant increase in glucagon level compared with the control, p< 0.05, Fig (4).

ACTH, corticosterone and insulin levels:

The results showed non significant change in their levels either

after one or three weeks of treatment by sertraline, in normal and diabetic groups, Fig (5,6,7).

Body weight:

The results showed non significant change in body weight both in normal and diabetic rats after one week and three weeks of sertraline treatment in normal and diabetic groups compared with the control, Fig (8).

Table (1): Effects of selective serotonin reuptake inhibitor sertraline on serum glucose, norepinephrine, epinephrine, ACTH, glucagon, corticosterone, insulin and body weight in normal and diabetic male albino rats (mean 6± SD)

Parameter	Normal groups			Diabetic groups		
	Control	One week sertraline treatment	Three week sertraline treatment	Control	One week sertraline treatment	Three weeks sertraline treatment
Glucose(mg/dl)	107.6±3.02	101.2± 1.99*	84.5± 5.31*	206±5.1	183.6±5.51*	164.1± 4.89*
Norepinephrine (pg/ml)	320±2.63	321.5±4.5	357.5±2.88*	278.5±2.73	275.8±7.02	342±5.84*
Epinephrine (pg/ml)	76.9±1.3	101.8±2.68*	146±2.11*	65.9±1.89	100±1.6*	127.8±1.72*
Glucagon (pg/ml)	73.7±1.55	72.4±1.11	101.3±1.73*	65±1.97	63.8±1.67	85.7±3*
ACTH (pg/ml)	19.2±0.59	19.5± 0.76	20.2±1.91	18.5±0.81	18.8±0.85	18.3±1.21
Corticosterone (ng/ml)	30.6±1.3	29.6±1.62	31.5±0.51	30.1± 0.94	30.1±1.43	30.7±1.68
Insulin (IU/dl)	11.6±0.78	11.5±0.54	11.5±0.53	7.3 ±0.33	7.6±0.45	7.4±0.25
Body weight (gm)	252±7.52	255±8.6	246.5±8.96	226.5±4.76	225.8±1.47	225.3 ±7.2

*= Denotes statistical significance

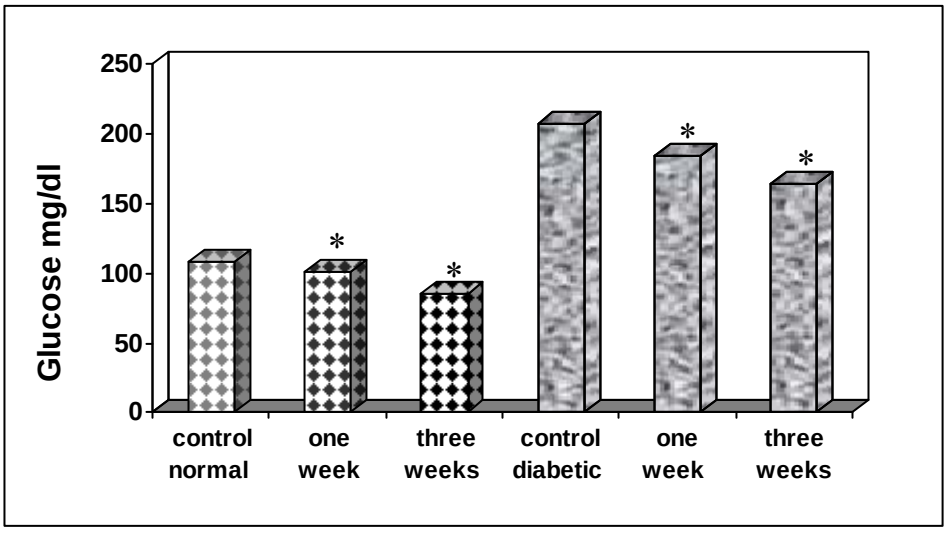

Fig (1): Effect of selective serotonin reuptake inhibitor sertraline on serum glucose (mg/dl) in normal and diabetic male albino rats.

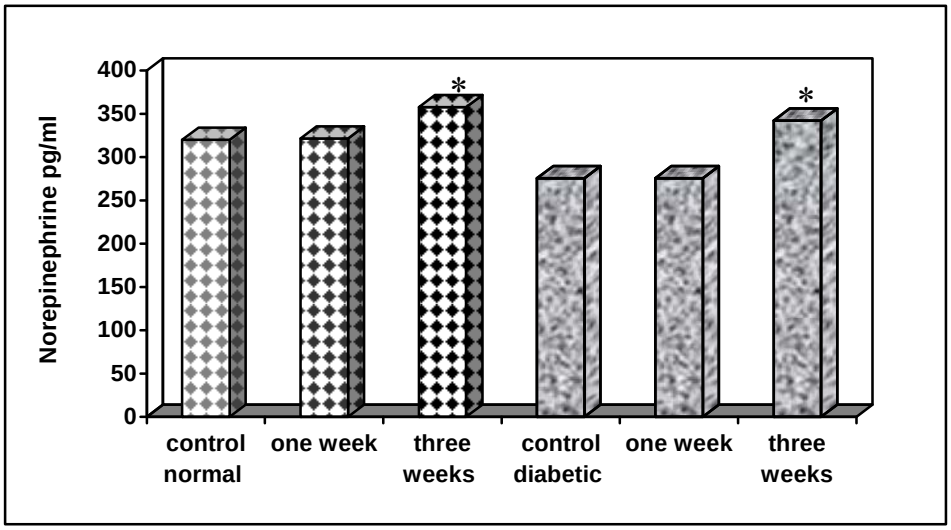

Fig (2): Effect of selective serotonin reuptake inhibitor sertraline on plasma norepinephrine (pg/ml) in normal and diabetic male albino rats

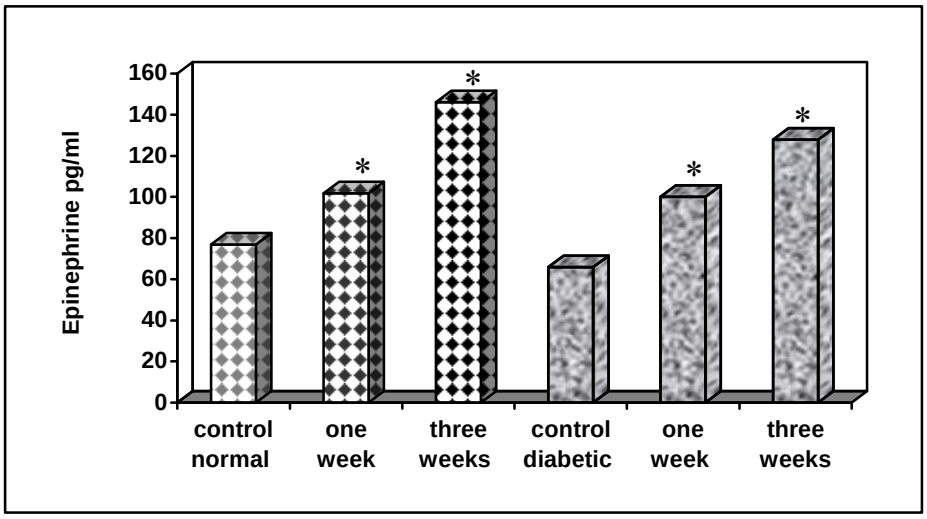

Fig (3): Effect of selective serotonin reuptake inhibitor sertraline on plasma epinephrine (pg/ml) in normal and diabetic male albino rats.

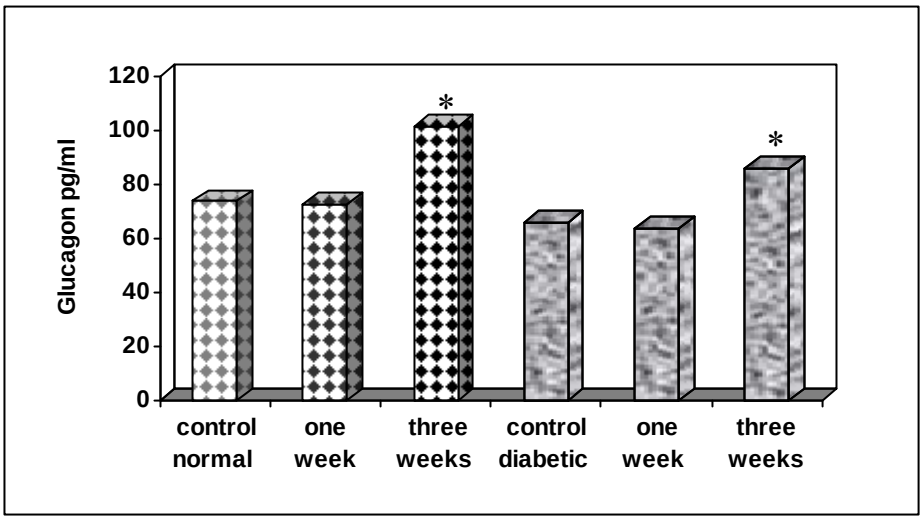

Fig (4): Effect of selective serotonin reuptake inhibitor sertraline on plasma glucagon (pg/ml) in normal and diabetic male albino rats.

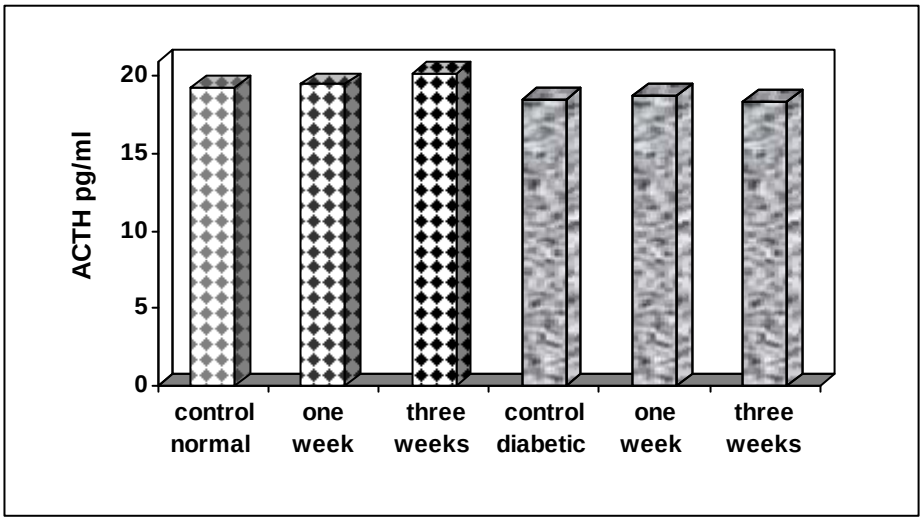

Fig (5): Effect of selective serotonin reuptake inhibitor sertraline on plasma ACTH (pg/ml) in normal and diabetic male albino rats.

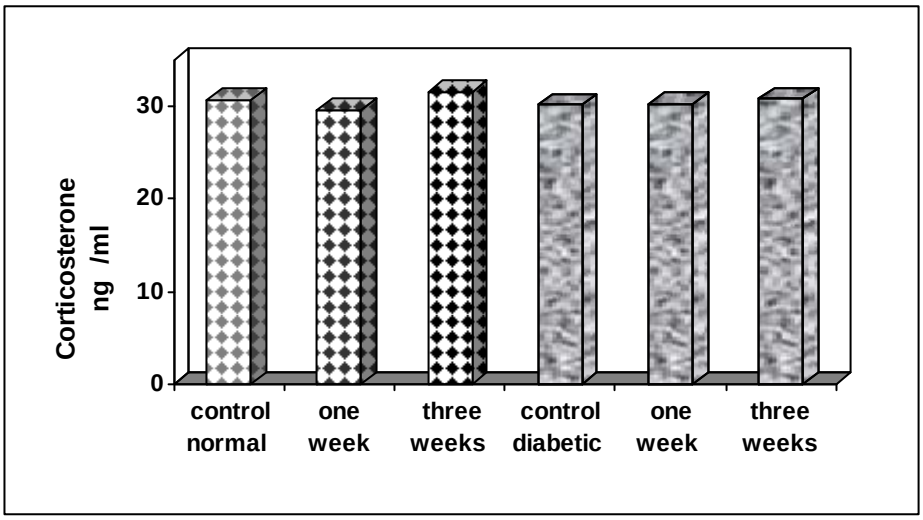

Fig (6): Effect of selective serotonin reuptake inhibitor sertraline on plasma corticosterone (ng/ml) in normal and diabetic male albino rats.

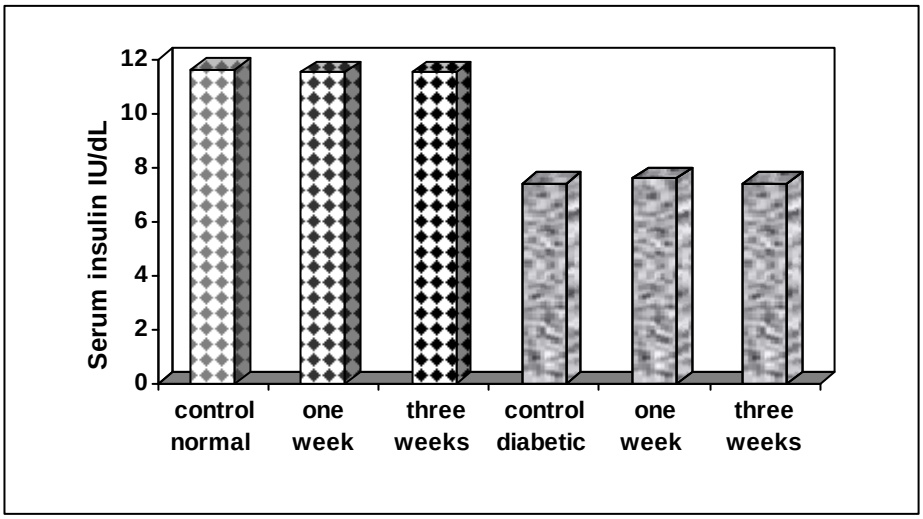

Fig (7): Effect of selective serotonin reuptake inhibitor sertraline on serum insulin (IU/dl) in normal and diabetic male albino rats.

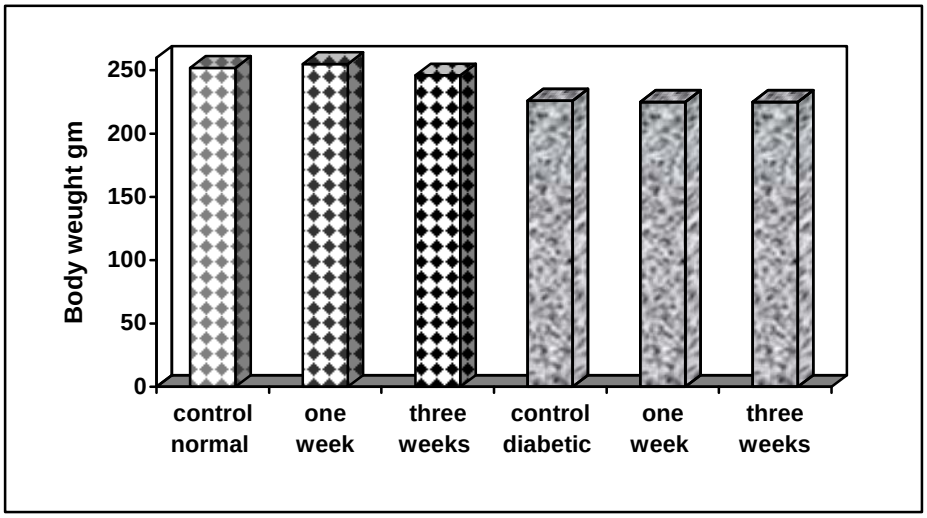

Fig (8): Effect of selective serotonin reuptake inhibitor sertraline on body weight (gm) in normal and diabetic male albino rats.

DISCUSSION

The use of selective serotonin reuptake inhibitors sertraline treatment in the diabetic patients is accompanied by intensive glucose lowering might exacerbate the risk of sever hypoglycemia[5]. The results of the present study showed that, continuous treatment with SSRI sertraline for three weeks, stimulated the release of epinephrine, norepinephrine and glucagon hormones. One week treatment by sertraline stimulated adrenomedullary response specifically, as there was no effect of sertraline on norepinephrine, glucagon, ACTH, corticosterone, insulin or body weight in normal and diabetic rats.[9]

The reduction of blood glucose without change in insulin level by SSRI sertraline, may be due to the effect of sertraline increased insulin sensitivity. It was reported that SSRIs caused rapid and significant elevation in hepatic glucose uptake and increased hepatic glycogen levels in presence of hyperinsulinemia, but not in normal insulin level[20]. Similarly, it was proved that, intra-portal infusion of serotonin[21], or 5-hydroxytryptophan[22] enhanced the net hepatic glucose uptake in dogs, which may be due to presence of multiple serotonin receptor subtypes which are expressed in the liver[23]. Furthermore, SSRIs treatment in mice was shown to reduce plasma glucose without changing in the insulin levels[24], which may be due to decreased intestinal absorption of glucose or increase peripheral insulin receptor sensitivity[12]. Moreover, it was observed in overweight patients with type 2-diabetes that, 4-weeks SSRIs treatment improved insulin-mediated glucose disposal[25]. The epinephrine secretion during sertraline treatment may be enhanced under conditions of stress (hypoglycemia), which may reflect the selective innervation and recruitment of adrenal chromaffin cell in response to various stressful stimuli[26]. The serotonergic effects on adrenomedullary activation may be due to systemic or central delivery of $5HT_{1A,}$ $5HT_{1c}$ or $5HT_2$ receptor agonists that increased epinephrine levels in a dose-dependent manner[27]. Also, caudal hindbrain serotonin neurons project to the spinal cord, synapse on sympathetic preganglionic neurons and innervate the adrenal medulla[28], so it is possible that, this population of serotonin neurons expresses the key glucose-sensing protein[11]. Moreover, it was reported that, direct application of glucoprivic agent, 5-thioglucose into hindbrain stimulates adrenomedullary secretion, glucagon, corticosterone and stimulate feeding response[29]. It is possible that SSRIs treatment modulated the response and sensitivity of serotonin on glucose-sensing neurons that control hormonal counterregulation to hypoglycemia[30]. It was observed that, the mechanism of action of SSRIs usually involved an increase in the synaptic concentration of serotonin, so it is possible that, sertraline stimulated epinephrine release in response to the hypoglycemic effect by direct action on the adrenal medulla, where both serotonin reuptake transporter

mRNA[31] and protein[32] are also localized in adrenal medullary chromaffin cells. Since tryptophan hydroxylase, the rate limiting enzyme in serotonin synthesis is not present in the adrenal medulla, so it is thought that serotonin is captured from the blood and accumulates in chromaffin cells via the serotonin reuptake transporter[32]. It was reported that mice lacking the serotonin reuptake transporter exhibit an exaggerated epinephrine response to stress[33]. It was observed that sertraline treatment was more effective in prolonged treatment (3 weeks), which may be related to the time course of SSRIs induced changes in serotonergic neurotransmission and signaling. Short treatment by SSRIs blocked the reuptake activity of serotonin transporter and increased synaptic levels of serotonin[34]. However SSRIs treatment more than 15 days reduced transporter binding, function, transporter mRNA, serotonin clearance and downregulation in postsynaptic receptors[35]. The enhancement of glucagon secretion after three weeks sertraline treatment may be secondary to the overall enhanced sympatho-adrenomedullary responses in three weeks treated rats[36]. It was observed that, there was no effect of sertraline treatment on ACTH or corticosterone. It is possible that sertraline-induced hypothalamic-pituitary-adrenal axis activation and C-*f*os expression become blunted by daily treatment. Also, the selective effect of sertraline on adrenomedullary activation without any alteration in ACTH or corticosterone, may be due to the specific action of sertraline on the adrenal medulla[37]. The results showed no effect of sertraline on body weight after one or three weeks treatment. It is possible that the anorectic action of sertraline had no effect on powerful feeding response due to glucose deficit. Also, chronic blockade of serotonin reuptake transporter does appear to modulate the neuronal circuitry required for the feeding response elicited by hypoglycemia[37]. This may be due to population of rostrally projecting hindbrain catecholamine neurons, whose activity and function may not be affected by sertraline[38].

Conclusion and recommendation:

It is concluded that, SSRI sertraline treatment produced hypoglycemia and increase adrenomedullary response. Also, sertraline treatment impacted the normal physiological responses to hypoglycemia, and masked the hypoglycemic symptoms especially during treatment of depression and diabetes. It is recommended to use sertraline for treatment of comorbid diabetes and depression, and to reduce the dose of antidiabetic drugs during sertraline treatment.

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تأثير مثبطات استرجاع السيروتونين سيرترالين على التنظيم الهرموني للجلوكوز في الدم في ذكور الفئران البيضاء السليمة والمصابة بمرض السكر

روميساء على الشربينى و محمد نبيه عبد الرحمن
قسم الفسيولوجيا و الفارماكولوجيا- كلية الطب-جامعة طنطا

يهدف هذا البحث إلى دراسة تأثير مثبطات استرجاع السيروتونين سيرترالين على التنظيم الهرمونى للجلوكوز في الدم في ذكور الفئران السليمة والمصابة بمرض السكر. وقد أجرى هذا البحث على ٣٦ فأرا وزنت ثم قسمت إلى مجموعتين.

المجموعة السليمة: وتشتمل على١٨ فارا ناضجا قسمت الى ثلاثة مجموعات

١- المجموعة الضابطة وقد أعطت محلول الملح عن طريق أنبوبة صغيرة بالفم
٢- المجموعة الثانية: أعطيت سيرترالين بجرعة ٣٠ مجم/كجم/يوم عن طريق أنبوبة صغيرة بالفم لمدة أسبوع.
٣- المجموعة الثالثة أعطيت سيرترالين بجرعة٣٠ مجم/كجم/ يوم عن طريق أنبوبة صغيرة بالفم لمدة ثلاثة اسابيع.

المجموعة المصابة بالسكر: وتشمل ١٨ فاراً وقد حقنت الفئران كلها بجرعة واحدة من الإستربتوزتوسين ٥٠مجم/كجم ثم قسمت الى ثلاث مجموعات

١- المجموعة الضابطة وقد أعطيت بمحلول الملح عن طريق أنبوبة صغيرة بالفم
٢- المجموعة الثانية: أعطيت سيرترالين بجرعة ٣٠ مجم/كجم/يوم عن طريق أنبوبة صغيرة بالفم لمدة اسبوع.
٣- المجموعة الثالثة أعطيت سيرترالين بجرعة ٣٠ مجم/ يوم عن طريق أنبوبة صغيرة بالفم لمدة ثلاثة اسابيع.

وفى نهاية البحث وزنت الفئران ثم ذبحت وجمعت عينات الدم لقياس مستوى الجلوكوز، والابينفرين، والنورأبينفرين، الجلوكاجون و الهرمون المنبه للغدة الكظرية، الكورتيكوستيرون، والانسولين.

وقد أظهرت نتائج البحث أن العلاج بسيرترالين قد سبب انخفاضا ملحوظا ذو دلالة احصائية في مستوى الجلوكوز بعد اسبوع وثلاثة اسابيع من العلاج فى الفئران السليمة والمصابة بمرض السكر. كما اظهرت النتائج ارتفاعا ملحوظا ذو دلالة احصائية فى مستوى هرمون الابينفرين بعد أسبوع وثلاثة أسابيع من العلاج فى الفئران السليمة والمصابة بالسكر. كما أن هناك ارتفاع ملحوظ فى مستوى النورابينفرين والجلوكاجون بعد ثلاثة اسابيع من العلاج فى الفئران السليمة والمصابة بالسكر كما اظهرت النتائج عدم تغير نسب كل من الهرمون المنبه للغده الكظرية، الكورتيكوستيرون، والانسولين ووزن الجسم.

ويستخلص من نتائج هذا البحث أن مثبطات استرجاع السيروتوتين سيراترالين تسبب نقص في مستوى الجلوكوز في الدم وتزيد من افراز نخاع الغدة الكظرية كما تسبب إخفاء لأعراض نقص الجلوكوز ولذلك ينصح باستعمال سيراترالين لمرضى الاكتئاب و السكر، كما ينصح بتقليل جرعة مخفضات السكر أثناء العلاج بسيراترالين عند مرضى السكر.