Metabolic and Behavioral Effects of Serotonergic Antidepressants in Rats Exposed to Swim Endurance Stress

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Abstract: Metabolic syndrome (MS) is a collection of risk factors for coronary artery disease and type 2 diabetes. Prevalence of the MS in patients with depression is high and use of antidepressants also exert variable effects on constituent elements of the MS. Metabolic and behavioral effects of chronic serotonergic antidepressants treatment in rats subjected to swim endurance test (SET) were investigated. The Albino Wistar rats were divided into 2 groups vehicle (n=12) and drug (n=12). Each group was further divided into unstressed and stressed. Tianeptine (20 mg/kg), and sertraline (30 mg/kg), was administered orally for 28 days. Results showed that tianeptine and sertraline treatment correspondingly increase rat swimming time in SET. Swim stress raised circulating glucose, non-esterified free fatty acids (NEFFA), cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and corticosterone levels with no effects on triglycerides (TGs). Drug alone administration showed that serum glucose levels were decreased by sertraline but not by tianeptine. Lipid levels were raised by both the drugs without effecting TGs. When drug treated stressed group was compared with the stressed controls, showed that tianeptine increases total cholesterol and LDL whereas TGs were decreased with no change on glucose levels. However sertraline treatment decreased the circulating glucose levels while the lipid profile remained unchanged. Corticosterone levels were increased by both the drugs. In conclusion, both the drugs may contribute potentially to the development of MS.It is suggested that antidepressant therapy should include routine surveillance for clinical and/or biochemical evidence suggestive of the metabolic syndrome.

Keywords: Swim endurance test, lipid profile, glycemic homeostasis, sertraline, tianeptine.

INTRODUCTION

Stress is a biological response to aversive conditions that tend to threaten or perturb the homeostasis of the organisms [1]. Stress has been shown to induce a marked rise in the brain levels of biogenic amines such as adrenaline and nor-adrenaline [2]. These chemical substances are released in response to stress signals and are meant to assist the organisms to cope with stress [3]. However, increased utilization of the amines resulting in their depletion in prolonged severe stress is responsible for fatigue, reduced stamina, lowered mood (depression) or despair seen in individuals under intense stress [2, 4]. Major depressive disorder is a prevalent medical syndrome associated with inter-episodic dysfunction. The metabolic syndrome is comprised of several established risk factors for cardiovascular disease (CVD) (i.e. abdominal obesity, dyslipidaemia, dysglycaemia and hypertension). The criteria of the metabolic syndrome represent a multi-dimensional risk factor for cardiovascular disease and type 2 diabetes mellitus. Extant evidence indicates that both major depressive disorder and the metabolic syndrome, though distinct, often co-occur [5]. It has been hypothesized [6] that altered central serotonergic function is causally related to the metabolic syndrome, and blunted serotonergic response is observed in individuals with the metabolic syndrome and insulin resistance.

Selective serotonin reuptake inhibitors (SSRIs) first appeared in the late 1980s (fluoxetine, sertraline-, paroxetine. fluvoxamine, citalopram escitalopram. This group of antidepressants has eclipsed all others because of their efficacy, ease of administration, including favorable cardiac side effect profile [7]. Compared with tricyclic antidepressants (TCAs) that block the reuptake of serotonin (5HT) and norepinephrine (NE), SSRIs are largely serotonin reuptake blockers and have little therapeutic effect on other neurotransmitters. SSRIs are much less likely than TCAs to cause fatalities (particularly cardiac deaths) in overdoses. Also, TCAs may be associated with an increased risk of myocardial infarction compared with SSRIs [8]. Among antidepressants that are currently available, selective serotonin reuptake inhibitors and possibly a few others with pronounced serotonin activity, appear to have the greatest potential for positively influencing cardiovascular health, independent of their effect on depression. Sertraline postulated mechanisms driving this association include serotonin mediated antiplatelet activity, and increased heart rate variability [9]. Besides 5HT reuptake inhibition, sertraline has dopamine reuptake inhibitor action and sigma opioid receptor antagonistic activity.

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The therapeutic effect of the drugs cannot be assessed in normal animals, unless the environment for drug action and the conditions to be restored by the drugs are created, in other words a biologically altered model is required to explore the therapeutic action of the drug, without which only the pharmacology can be checked [10]. Numerous animal models of stress and depression are in use by researchers to screen the therapeutic activity of the drug, namely, restraint stress model, foot shock, tail suspension, forced swim stress (FST) and the swim endurance test (SET). Though physical activity promotes glucose uptake independent of insulin action [11], the central nervous system (CNS) alterations caused by these models play a major role in development of behavioral despair. SET model has been used previously by researchers to explore the adaptogenic activity of various compounds [12-14], the original method of Nimbakar and coworkers, 2001 was followed [15]. Tricyclic antidepressant (TCA) use also increased likelihood for the metabolic syndrome, independent of depression severity [16]. Some SSRIs are also associated with clinical and biochemical elements of the metabolic syndrome [17]. An interesting clinical observation is that psychotropic agents, particularly antidepressant drugs, commonly affect the cardiovascular system and drugs used to treat heart disease commonly affect the CNS. Perhaps, the roles played by serotonin, norepinephrine, and dopamine in both depression and CVD account for this finding. The connection between changes in lipid and glucose homeostasis, corticosterone and long-term administration of therapeutically effective doses of tianeptine, a selective serotonin reuptake enhancer (SSRE) and sertraline (SSRI) that are potent antidepressants has not been suffciently demonstrated so far. Therefore, we analyzed the effects of chronic administration of serotonergic antidepressants on behavior in SET paradigm, serum glucose, corticosterone and lipid levels which are risk factors for cardiovascular disease in depressive patients.

MATERIALS AND METHODS

Animals and Treatment

All animal procedures described below were conducted in strict accordance with the national research council for the care and use of laboratory animals (1996). Ethical approval was obtained from institutional animal ethics committee. Locally bred Adult Albino Wistar rats (150-200 g body wt.) were housed 6 per cage under standard light and dark cycle at 25^{o}C ± 2^{o}C room temperature and were maintained on lab chow and water ad libitum. All experiments were carried out in the light phase of the cycle. All experiments were carried out with minimum suffering to the animals. Rats were checked for open field locomotor activity. Tianeptine (20 mg/kg/ml) and sertraline (30mg/kg/ml) was orally administered to the test group for 4 weeks. An equal volume of vehicle (ethanol: saline, 1:3) was given to the controls. Rats were decapitated on the day following treatment completion. The rats of the SET group were made to swim till exhaustion (indicated as when the rat was about to drown), an average of 30 minutes swimming before decapitation. Serum was collected and stored at -20^{o}C until analysis.

Swim Endurance Test (SET)

The animals were forced to swim in a transparent glass chamber (80 cm high and 45cm inner diameter), filled with tap water, 45 cm deep at room temperature. The water temperature was strictly maintained at 30^{0}-32^{0}C and none of the animals experienced hypothermia, which could be additional stress. The rats were allowed to swim till they got exhausted and the moment they drowned was considered the end point [15]. The end point of the rats was an average of 30 minutes.

Chemicals and Drugs

Tianeptine Sodium salt (Sigma-Aldrich) and Sertraline HCl (a kind gift from a local pharmaceutical) were used for the present study. All chemicals were of the highest analytical grade.

Biochemical Analysis

Serum total Cholesterol, high-density lipoproteins (HDL) and triglycerides were determined by Randox® Kit. Low-density lipoproteins cholesterol was determined by formula. Glucose levels were estimated by *o*-toulidine method. Non esterified free fatty acid (NEFFA) was estimated by the method of Mikac- Devic (1973) using separate solutions of copper nitrate and triethanolamine that were mixed before use. Copper soaps are formed with the fatty acids and are determined using 1, 5- diphenylcarbohydrazide as a color developing reagent at 628nm [18]. Corticosterone was quantified by Glick *et al.*, 1964. The procedure is based on organic extraction of corticosterone with iso-octane and chloroform. Fluorescence developed by ethanol-sulphuric acid solution was measured at excitation (462nm) and emission (518 nm) wavelengths [19].

Statistical Analysis

All results were expressed as mean ± standard error of mean (SEM). Data was analyzed using two way ANOVA followed by Newman Keul's q-test. P< 0.05 was considered statistically significant. The analysis was carried out using SPSS software version 19.

RESULTS

Table **1** shows the effects of serotonergic drugs on swimming endurance in minutes. Data analyzed by student's t-test indicates that swimming time was significantly increased by tianeptine (P = 0.0005) and sertraline (P = 0.0005).

Table 1: Effect of Serotonergic Antidepressants on Swimming Time in Rats Exposed to Swim Endurance Test

Groups	Mean
Vehicle	10.66± 2.2
Tianeptine	24.03 ± 2.1*
Vehicle	11.62± 1.5
Sertraline	22.06 ± 3.2†

Experimental details are given in materials and methods section. Values are means± SEM for each group of 6 rats. Statistical analysis was carried out using student's t-test. The significance of the differences is indicated by *P=0.0005 when drug treated groups were compared with respective saline controls.

Table **2** shows the effects of tianeptine on serum glucose, NEFFA and Lipid profile. Data analysed by 2 way analysis of variance show significant effects of stress on serum glucose (F=10.94, P=0.004), NEFFA (F=7.89, P=0.011), cholesterol (F=5.84, P=0.025), and on TG levels (F=10.81, P=0.004), whereas aninsignificant change was seen in HDL and LDL levels. Similarly significant effects were seen by drug on serum NEFFA (F=38.35, P=0.0005), cholesterol (F=53.78, P=0.0005), HDL (F=6.35, P=0.02), TGs (F=7.57, P=0.012) and on LDL levels (F=30.59, P=0.0005). Stress x drug effects were significant on NEFA (F=16.18, P=0.001), cholesterol (F=10.45, P=0.004), HDL (F=9.57, P=0.006) and TGs (F=18.08, P=0.0005) while insignificant effects on glucose and LDL levels were seen.

Table **3** shows the effects of sertraline on serum glucose, NEFFA and Lipid profile. Data analysed by 2 way analysis of variance show significant effects of stresson serum glucose (F=6.91, P=0.0005), NEFFA (F=22.5, P=0.0005), cholesterol (F=8.36, P=0.009) and on LDL levels (F=4.86, P=0.039, whereas a significant change was seen in HDL & TG levels. Similarly significant effects were seen by drug on serum glucose (F=327.94, P=0.005), NEFFA (F=30.56, P=0.0005), cholesterol (F=7.18, P=0.014), HDL (F=16.64, P=0.001), and on LDL levels (F=12.99, P=0.002) stress x drug effects were significant on glucose (F=13.67, P=0.0005), NEFFA (F=18.03, P=0.0005), cholesterol (F=7.99, P=0.01), HDL (F=23.00, P=0.0005) while insignificant effects on TGs and LDL were seen.

Figures **1** shows the effect of tianeptine on serum corticosterone levels. Data analyzed by 2-way ANOVA

Table 2: Effects of Tianeptine Administration on Serum Glucose, NEFFA and Lipid Profile

	Vehicle		Drug		2 way ANOVA		df=1,20
Parameters	**Unstressed**	**Stressed**	**Unstressed**	**Stressed**	**Stress**	**Drug**	**Stress x drug**
Glucose (mg/ dl)	160.95 ± 15.03	210.66 ± 12.36*	157.11 ± 12.88	188.71 ± 17.72	F=10.94 P=0.004	F=1.09 (NS)	F=0.55 (NS)
NEFFA (mM/l)	0.48 ± 0.02	0.61 ± 0.04*	0.85 ± 0.02 †	0.81 ± 0.05	F=7.89 P=0.011	F=38.35 P=0.0005	F=16.18 P=0.001
Cholesterol (mg/dl)	80.58 ± 2.91	120.20 ± 7.64*	154.71 ±10.2 †	148.98 ± 7.69†*	F=5.84 P=0.025	F=53.78 P=0.0005	F=10.45 P=0.004
HDL (mg/dl)	42.21 ± 2.52	62.3 ± 2.86*	67.43 ± 6.84 †	54.31 ± 3.55	F=0.58 (NS)	F=6.35 P=0.02	F=9.57 P=0.006
TGs (mg/dl)	64.68 ± 2.53	69.94 ± 3.22	72.60 ± 4.2	35.62 ± 1.89 † *	F=10.81 P=0.004	F=7.57 P=0.012	F=18.08 P=0.0005
LDL (mg/dl)	25.32 ± 1.91	43.98 ± 6.86	72.76 ± 3.02 †	88.03 ± 3.63 †	F=4.21 (NS)	F=30.59 P=0.0005	F=0.042 (NS)

Experimental details are given in materials and methods section. Values are means± SEM for each group of 6 rats Data was analysed using 2-way ANOVA followed by Newman kuel's q test. The significance of the differences is indicated by *P<0.05 when stressed group is compared with respective control and †P<0.05 when drug treated group is compared with similarly treated vehicle control.

Table 3: Effects of Sertraline Administration on Serum Glucose, NEFFA and Lipid Profile

	Vehicle		Drug		2 way ANOVA		df=1,20
Parameters	**Unstressed**	**Stressed**	**Unstressed**	**Stressed**	**Stress**	**Drug**	**Stress x drug**
Glucose (mg/ dl)	192.10 ± 14.05	248.38 ± 10.83*	163.92 ± 10.23 †	154.41 ± 13.55 †	F=6.914 P=0.0005	F=327.94 P=0.0005	F=13.67 P=0.0005
NEFFA (mM/L)	0.27 ± 0.07	1.01 ± 0.3*	1.08 ± 0.08 †	1.12 ± 0.07	F=22.5 P=0.0005	F=30.56 P=0.0005	F=18.03 P=0.0005
Cholesterol (mg/dl)	84.13 ± 5.03	140.61 ± 10.51*	138.52 ± 11.66 †	139.15 ± 11	F=8.36 P=0.009	F=7.18 P=0.014	F=7.99 P=0.01
HDL (mg/dl)	33.91 ± 1.14	56.05 ± 1.95*	64.10 ± 2.28 †	54.23 ± 2.9	F=0.83 (NS)	F=16.64 P=0.001	F=23.00 P=0.0005
TGs (mg/dl)	59.75 ± 7.71	69.45 ± 6.82	51.95 ± 6.60	70.38 ± 5.85	F=2.49 (NS)	F=0.15 (NS)	F=0.24 (NS)
LDL (mg/dl)	26.31 ± 2.6	46.31 ± 2.61*	56.63 ± 4.2 †	56.73 ± 8.88	F=4.86 P=0.039	F=12.99 P=0.002	F=2.61 (NS)

Experimental details are given in materials and methods section. Values are means± SEM for each group of 6 rats. Data was analysed using 2-way ANOVA followed by Newman kuel's q test. The significance of the differences is indicated by *P<0.05 when stressed group is compared with respective control and †P<0.05 when drug treated group is compared with similarly treated vehicle control.

indicates that the effect of tianeptine (F=98.88, P=0.0005) and stress x drug interaction (F=26.99, P=0.0005) was significant.

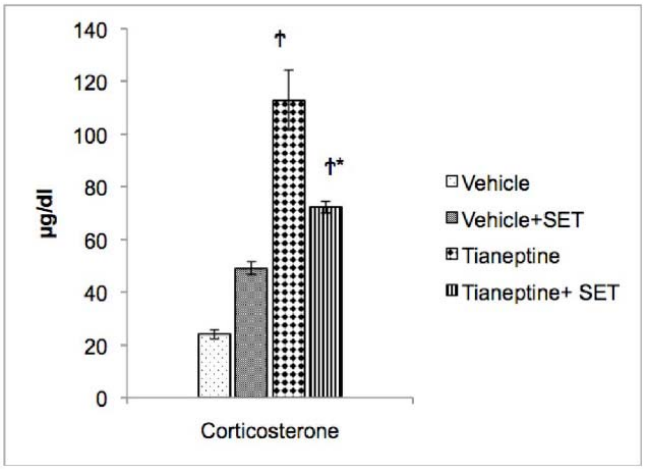

Figure 1: Effect of Tianeptine administration on serum corticosterone. Data was analysed using 2-way ANOVA followed by Newman's kuel's q test. Values are means± SEM for each group of 6 rats. The significance of the differences is indicated by *P<0.05 when stressed group is compared with respective control and †P<0.05 when drug treated group is compared with similarly treated vehicle control.

Figure **2** shows the effect of tianeptine on serum corticosterone levels. Data analyzed by 2-way ANOVA indicates that the effect of stress (F=9.09, P=0.007) and drug (F=294.17, P=0.0005) was significant.

DISCUSSION

The swimming time was equally increased by both the drugs during the swim endurance test (SET). It has been observed by Bano and group in 2010 [20], acute administration of 10mg/kgdose of tianeptine, sertraline raises brain tryptophan levels, thus serotonin. Antidepressants drugs may act in part by enhancing serotonergic activity. The serotonergic deficit may occur at any of several levels: diminished availability of precursor, impaired activity of tryptophan hydroxylase, abnormalities in 5-HT release or uptake, 5-HT receptor abnormalities or interaction with other neurotransmitters. Cerebral 5-hydroxytryptamine (serotonin, 5-HT) synthesis is controlled mainly by

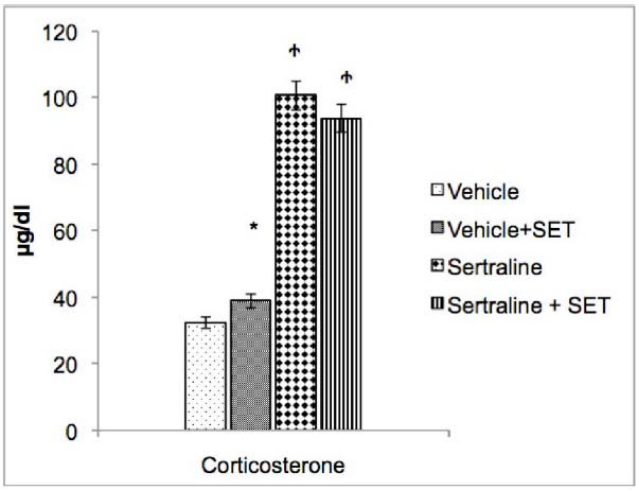

Figure 2: Effect of Sertraline administration on serum corticosterone. Data was analysed using 2-way ANOVA followed by Newmankuel's q test. Values are means± SEM for each group of 6 rats. The significance of the differences is indicated by *P<0.05 when stressed group is compared with respective control and †P<0.05 when drug treated group is compared with similarly treated vehicle control.

brain tryptophan concentrations, because the rate limiting enzyme of the 5-HT biosynthetic pathway, tryptophan hydroxylase, is unsaturated with its substrate (tryptophan). This process is determined by at least three peripheral factors influencing circulating tryptophan availability to the brain that play important roles in central 5-HT synthesis. These factors include tryptophan binding to circulating albumin, competition between tryptophan and large neutral amino acids (LNAA), namely valine, leucine, isoleucine, phenylalanine & tyrosine for cerebral uptake [21] and activity of the major tryptophan degrading enzyme, liver tryptophan 2,3 dioxygenase activity.

Drugs that elevate mood (antidepressants) have profound interactions with the HPA axis. The use of antidepressants is on the rise with the rising incidence of depression in the general population all over the world currently. Long term antidepressant treatments are associated with metabolic disorders, obesity and insulin resistance, leading ultimately to cardiovascular disorders, besides the proposed effects of antidepressants that include, neurogenesis [22, 23], strengthened neuroplasticity [24] and attenuation of HPA axis to stress [25]. It has been concluded in a study that the relationship between antidepressants and diabetes type 2 is biologically implausible and may be based on overestimations [26]. Hummel and coworkers concluded through a randomized open-label prospective trial that remission from depression with antidepressant treatment improves the LDL/HDL cholesterol ratio, shifting the lipoproteins towards a lesser atherogenic profile [27]. Paroxetine and sertraline have been found to increase the LDL levels in the serum [28, 29]. Sauer and coworkers reported that the percentage of occurrence of hypercholesterolemia in antidepressant users is higher than the non-users [30]. Colotto and coworkers have highlighted a collective conclusion that sertraline and paroxetine have an unfavorable effect on the lipid profile in contrast to citalopram that shows a slight increase in HDL cholesterol with no effect on total cholesterol and LDL levels [31]. In a case report, citalopram and to a lesser extent fluoxetine were suspected to cause severe hypertriglyceridemia [32]. Wei and coworkers, in 2009 concluded through a cohort study that long-term use of paroxetine or sertraline may have a measurable adverse impact on cardiovascular risk in adults [33]. To normalize the metabolic hypo activity, caused by depression the energy pathways are worth pursuing [34]. It can be sparingly explained that adjustment of central monoamine levels is not the only way to treat mental disorders; in fact peripheral involvement plays a major role in alleviation of depression. Present study shows (Table **2**) that tianeptine does not modulate serum glucose levels. The serum free fatty acids are elevated, probably due to the lipolytic effect of corticosterone. HDL are raised with tianeptine treatment. Drug induced rise in LDL which is highly significant, suggests desensitization of hepatic lipoprotein receptors rendering greater availability of the lipoprotein for steroidogenesis. No change in the Triglyceride levels is found with tianeptine treatment in unstressed rats. However there was significant decrease in TG in drug treated stressed rats.

Sertraline is a glucose lowering drug, accompanied with elevated circulating free fatty acids. Cholesterol as well as HDL and LDL are raised by sertraline. TGs remain unaltered with sertraline treatment. Previously, in 2001, Gomez and coworkers declared sertraline (30mg/kg) to be a drug that reduces glucose levels due to its effect on glucose induced insulin release [35]. Since serotonin and insulin are co-localized in the pancreatic beta cells, insulin is accompanied with serotonin when released [36]. High insulin levels by sertraline administration without hypoglycemia led to the presumption of the involvement of hepatic insulin sensitizing substance (HISS) secreted from the liver, responsible for the uptake and storage of glucose as glycogen in large skeletal muscles. It is suggested that sertraline prevents HISS secretion, increasing release of insulin to regulate glucose levels [37].

Since endurance training is known to enhance responsiveness to insulin and uptake of glucose into the muscles by increasing the expression of GLUT 4 (the insulin dependent transporters that are responsible for the uptake of glucose by the muscles, heart and skeletal muscles) [38], the rise in glucose levels of rats subjected to swim endurance test may be explained as a consequence of increased mobilization of glucose from storage depots along with enhanced uptake. Tianeptine does not modulate serum glucose levels in the stressed group, suggesting the presence of simultaneous mechanisms to counter act any change in the glycemic homeostasis that may be caused by stressful conditions. Stress as well as tianeptine induced rise in free fatty acids remained unaltered when the drug treated rats were subjected to the endurance test. The rise in cholesterol levels of the drug treated stressed group was greater than the untreated stressed group, though the levels were reduced as compared to the drug treated unstressed

group. The increase in the HDL levels of the drug administered stressed group was similar to the stressed as well as drug treated unstressed group. The triglyceride level remained unchanged by stress as well as tianeptine, though the level declined when the drug treated group was subjected to SET. The decline in TGs in the SET subjected group can be suggested to have a correlation with the lowered corticosterone levels in the same group. Endurance session with its effect on glucose mobilization and uptake may have a counter effect on the HPA axis activity, lowering circulating corticosterone. As glucocorticoids have the ability to potentiate the lipolytic action of epinephrine by its action on hormone sensitive lipase promoting re-esterification of free fatty acids,low levels of glucocorticoids may be the cause of low levels of circulating TGs. The rate of glucocorticoid induced lipolysis or lipogenesis can be determined with the help of available glycerol for gluconeogenesis.

Sertraline lowered the glucose levels in the drug treated stressed group as well. Stress induced rise in cholesterol, HDL and LDL remained unchanged in the sertraline treated stressed rats. It can be finally concluded that in spite of the hyper activation of the HPA axis that is obvious with stress, the adaptation process is enhanced by the drugs assessed in the present study and is observed as a regulated mobilization and utilization of energy molecules preventing the possible development of hyperglycemia and insulin resistance. The rise in circulating LDL levels with tianeptine raise doubts whether prolong treatment is safe in preventing the allostatic load to the users.

In conclusion, both the drugs may contribute potentially to the development of MS. It is suggested that antidepressant therapy should include routine surveillance for clinical and/or biochemical evidence suggestive of the metabolic syndrome.

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