ALLOXAN-INDUCED DIABETES POTENTIATES ANTIDEPRESSANT ACTIVITY IN RATS

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Summary

The objective of this study was to study the antidepressant activity of imipramine, amitryptiline, fluoxetine, and trazodone in alloxan-induced diabetes in rats The acute and chronic effects of imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.] were studied in different glycemic conditions using forced swim test, tail suspension test and reserpine antagonism. Antidepressant treatment resulted in a significant ($P<0.05$) increase in blood glucose level in mice and significantly ($P<0.05$) decreased total duration of immobility in all acute studies. A significant correlation between blood glucose level and antidepressant activity was observed in forced swim test and tail suspension test in euglycemic and hyperglycemic conditions. Antidepressants in combination with alloxan resulted in significant ($P<0.05$) increase in blood glucose level and significantly ($P<0.05$) decreased duration of immobility. Antidepressants significantly ($P<0.05$) antagonized reserpine induced hypothermia. The study reveals a good correlation between blood glucose level and antidepressant activity amongst various antidepressants.

KEY WORDS: Antidepressants, blood glucose level, alloxan, reserpine, forced swim test, tail suspension test

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Introduction

Depression is a common psychiatric illness comprising about 10% of all adult patients seeking medical attention (1) and it is known that antidepressants increase synaptic levels of noradrenaline, serotonin and in some cases dopamine (2). Catecholamines produce hyperglycemia by activation of phospholipase in liver by increasing cyclic AMP and intracellular ca^{++} levels 93). Antidepressants like tricyclic antidepressants (4), selective serotonin reuptake inhibitors (5), and drugs modulating serotonergic and adrenergic transmission (6) are known to increase blood glucose level. Experimental evidence confirms that there are "glucoreceptors" which are sensitive to changes in blood glucose level and regulate glucose utilization in the hypothalamus (7).

Stimulation of muscarinic, histaminergic, and serotonergic receptors increases hypothalamic noradrenergic neural activity, which is associated with hyperglycemia (8). Central GABA receptors play an inhibitory role in the regulation of hepatic glucose metabolism and elevated levels of GABA have been found in insulin treated animals (9). Diabetes with major depression has a very high rate of recurrent depressive episodes (10). Depression is associated with hyperglycemia in patients with Type 1 or Type 2 diabetes (11). There is also a suggestion that stress associated with depression may lead to hyperglycemia in diabetes (12).

The findings of Sevak et al., (13) that haloperidol is less potent to produce catalepsy in diabetic rats is consistent with reports of altered dopamine receptor binding in diabetes. Antidepressants are known to reduce haloperidol-induced catalepsy (14). However, it is not known whether there exists a correlation between blood glucose level and antidepressant activity. Therefore we assessed antidepressant activity of various clinically used antidepressants in normal, hypoglycemic and hyperglycemic rats using behavioral despair test, tail suspension test, and reserpine antagonism.

Materials and Methods

Drugs

alloxan (Burgoyne Burbidges Co., Mumbai), imipramine (Torrent Pharmaceuticals, Ahmedabad), amitryptiline (Torrent Pharmaceuticals, Ahmedabad), fluoxetine (Cadila Laboratories, Ahmedabad), trazodone (Sun Pharma, Mumbai), and reserpine (Hindustan Ciba-Geigy Ltd. Mumbai), were used for the study.

Animals

Male albino mice (20-25 g) and male albino rats (150-200 g) were obtained from Krishana Institute of Medical Science, Karad. Animals were housed in groups of five per cage under standard laboratory conditions with food and water *ad libitum*. A 12: 12h (light: dark) cycle was used with the light from 07:00 to 19:00 h. All behavioral testing was done during the day-light period preferably between 10:00 and 13:00. Animals were handled daily for 5 min during the last 3 days before the experiment.

Induction of hypoglycemia

Since physiological stress (swimming in water for 3 min) induces hypoglycemia (15) mice were allowed to swim individually for 3 min in a glass container (height 40 cm; diameter 15 cm) containing 10 cm of water, maintained at 25^{o}C. At the end of swimming, mice were removed from water, wiped gently with a clean dry towel. The presence of hypoglycemia was confirmed by measuring blood glucose level and 15 min later, mice were subjected for testing of antidepressant activity. Blood sugar level was measured using one touch strip glucometer (Johnson & Johnson Co. Mumbai).

Induction of hyperglycemia

Intraperitoneal administration of dextrose (2 g/kg) produces significant hyperglycemia (16). The presence of hyperglycemia was confirmed by measuring blood glucose level 30 min after dextrose and then mice were subjected for testing of antidepressant activity.

Alloxan induced diabetes

Alloxan (200 mg/kg, s.c) was used to induce diabetes (17). Blood was obtained from retro- orbital plexus with minimum stress and blood glucose levels were measured using glucometer. Antidepressant activity was assessed 24 h after alloxan treatment using forced swim test.

Measurement of antidepressant activity

Forced swim test

Mice were placed individually into a glass cylinder (height 40 cm; diameter 15 cm) containing 10 cm of water, maintained at 25^{o}C. After 10 min they were removed to a drying room (30^{o}C) for 30 min. Next day mice were placed in the same cylinder and the total duration of immobility was measured during 5 min test period as described earlier (18). Imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.) were administered 40 min before the test. All drugs were administered orally for 15 days in chronic studies and the test was carried out 40 min after the last administration.

Tail suspension test

Immobility was induced by tail suspension according to the procedure of Steru *et al*. (19). Albino mice were hung individually on a plastic string, 75 cm above the table top with an adhesive tape placed 1 cm from the tip of the tail. Duration of immobility was recorded for 7 min, discarding the movements in the first two minutes. Mice were considered immobile only when they hung passively and remained completely motionless. Imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.) were administered 40 min before the test. All drugs were administered orally for 15 days in chronic studies and the test was carried out 40 min after the last administration.

Reserpine antagonism

Reserpine (3 mg/kg, i.p.) was administered to rats half an hour after imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.). Rectal temperature was noted using telethermometer at 60, 90, 120, 180, 210, and 240 min. Blood glucose level was estimated after 1 h of antidepressant treatment (20).

Statistical Analysis

All data are expressed as mean ± SEM. The parametric data was analysed by one-way analysis of variance (ANOVA) followed by Dunnett's test and the non-parametric data was analyzed by Kruskal-Wallis test followed by Dunn's test. $P<0.05$ was considered significant.

Results

Forced Swim test

In vehicle treated mice (euglycemic condition), the difference in blood glucose level was found to be 4.66 ± 1.15 mg/dl and total duration of immobility was observed to be 87.25 ± 0.80 sec. Treatment with imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.) increased blood glucose level ($P<0.05$) from the initial level and decreased total duration of immobility ($P<0.05$) [Table1]. Correlation coefficient between difference in blood glucose level and duration of immobility was observed to be 0.91.

Table 1: Effect of acute and chronic treatment of various antidepressants on blood glucose level and duration of immobility in euglycemic condition in forced swim test using mice

Treatment (mg/kg)	Difference in blood glucose level (mg/dl)		Duration of immobility (sec) 40 min after treatment	
	Acute	Chronic	Acute	Chronic
Vehicle	4.66 ± 1.15	5.76 ± 1.55	87.25 ± 0.80	90.25 ± 0.80
Amitryptiline (10)	67.50 ± 9.61*	41.75 ± 3.35*	34.75 ± 1.88*	27.5 ± 0.64*
Imipramine (10)	43.50 ± 0.75*	18.5 ± 1.32*	57.75 ± 2.93*	45.5 ± 0.64*
Fluoxetine (10)	35.25 ± 5.79*	13.0 ± 0.92	65.75 ± 1.70*	55.25 ± 1.10*
Trazodone (10)	42.0 ± 1.22*	- 25.2 ± 3.10*	73.33 ± 2.09*	82.5 ± 1.10*
$F_{(4,20)}$	19.67	117.26	95.23	873.3

n = 5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* $P < 0.05$ as compared with vehicle group.
Correlation between BGL and duration of immobility (acute) = -0.91
Correlation between BGL and duration of immobility (chronic) = -0.8

In chronic treatment, the difference in blood glucose level was found to be 8.66 ± 1.15 mg/dl and total duration of immobility was observed to be 90.25 ± 0.80 sec in mice treated with vehicle. Treatment with imipramine (10 mg/kg, i.p), and amitryptiline (10 mg/kg, i.p) resulted in increased blood glucose level ($P<0.05$) from the initial level and total duration of immobility was decreased ($P<0.05$).Chronic treatment with fluoxetine (10 mg/kg, i.p.) showed an insignificant increase in blood glucose level ($P>0.05$) from initial level and the total duration of immobility was decreased ($P<0.05$). Chronic treatment of trazodone (10 mg/kg, i.p.) resulted in decreased blood glucose level ($P<0.05$) from the initial level and decreased duration of immobility ($P<0.05$) [Table1]. Correlation coefficient between difference in blood glucose level and duration of immobility was observed to be 0.8.

In hyperglycemic condition the difference in blood glucose level was found to be 26.0 ± 2.19 mg/dl and total duration of immobility was observed to be 77.75 ± 1.49 sec. Treatment with imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), and fluoxetine (10 mg/kg, i.p), increased blood glucose level ($P<0.05$) from the initial level and decreased total duration of immobility ($P<0.05$). Trazodone (10 mg/kg, i.p.) treatment resulted in an insignificant increase in blood glucose level compared to vehicle treated mice but resulted in decreased duration of immobility [Table 2]. Correlation coefficient between increase in blood glucose level and duration of immobility was observed to be 0.86.

Table 2: Effect of various antidepressants on blood glucose level and duration of immobility in hyperglycemic condition (pretreatment with 5% Dextrose- 2 gm/kg) in forced swim test using mice

Treatment (mg/kg)	Difference in blood glucose level (mg/dl)	Duration of immobility (sec) 40 min after treatment
Vehicle	26.0 ± 2.19	77.75 ± 1.49
Amitryptiline (10)	132.0 ± 16.35*	25.25 ± 1.65*
Imipramine (10)	71.75 ± 4.28*	31.5 ± 1.52*
Fluoxetine (10)	62.75 ± 1.25*	44.37 ± 3.87*
Trazodone (10)	40.0 ± 0.81	53.5 ± 2.69*
$F_{(4,20)}$	28.51	72.40

n=5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* $P < 0.05$ as compared with vehicle group.
Correlation between BGL and duration of immobility = -0.86

In alloxan treated mice, blood glucose level was observed to be 189.0 ± 3.24 mg/dl and total duration of immobility was observed to be 77.5 ± 1.79 sec. Treatment with imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.) in combination with alloxan increased blood glucose level ($P<0.05$) and decreased total duration of immobility ($P<0.05$) [Table 3]

Table 3: Effect of various antidepressants on blood glucose level and duration of immobility in diabetic condition (pretreatment with alloxan- 200 mg/kg) in forced swim test using mice

Treatment (mg/kg)	Blood glucose level 30 min after treatment (mg/dl)	Duration of immobility (sec) 40 min after treatment
Vehicle	96.75 ± 11.66	87.25 ± 9.73
Alloxan (200)	189.0 ± 3.24*	77.5 ± 1.79
Amitryptiline (10)	144.75 ± 3.83*	34.75 ± 1.88*
Alloxan + Amitryptiline (200) (10)	288.75 ± 4.87#	22.75 ± 0.85#
Imipramine (10)	127.25 ± 1.94*	57.75 ± 2.93*
Alloxan + Imipramine (200) (10)	267.5 ± 4.83 #	36.25 ± 1.79#
Fluoxetine (10)	126.75 ± 4.11*	65.75 ± 1.70*
Alloxan + Fluoxetine (200) (10)	241.0 ± 3.48#	57.0 ± 1.82#
Trazodone (10)	121.0 ± 10.7*	73.33 ± 2.09*
Alloxan + Trazodone (200) (10)	244.5 ± 3.24#	37.25 ± 0.85#
$F_{(9,40)}$	135.11	36.61

n=5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* $P < 0.05$ as compared with vehicle group, # $P < 0.05$ as compared with alloxan group. Correlation between BGL and duration of immobility = -0.718

Tail suspension test

In vehicle treated mice (euglycemic condition), the difference in blood glucose level was found to be 8.75 ± 3.75 mg/dl and total duration of immobility was observed to be 192.25 ± 5.0 sec. Treatment with imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.) increased blood glucose level ($P<0.05$) from the initial level and decreased total duration of immobility ($P<0.05$) [Table 4]. Correlation coefficient between difference in blood glucose level and duration of immobility was observed to be 0.6.

In chronic treatment, the difference in blood glucose level was found to be 12.12 ± 3.75 mg/dl and total duration of immobility was observed to be 194.75 ± 2.68 sec in mice treated with vehicle. Treatment with amitryptiline (10 mg/kg, i.p.) resulted in increased blood glucose level ($P<0.05$) from the initial level and total duration of

immobility was decreased (P<0.05). Chronic treatment with imipramine (10 mg/kg, i.p.), and fluoxetine (10 mg/kg, i.p.) showed an insignificant increase in blood glucose level (P>0.05) from initial level and the total duration of immobility was decreased (P<0.05). Chronic treatment of trazodone (10 mg/kg, i.p.) resulted in decreased blood glucose level (P<0.05) from the initial level and decreased total duration of immobility (P>0.05) [Table 4]. Correlation coefficient between difference in blood glucose level and duration of immobility was observed to be - 0.8.

Table 4: Effect acute and chronic treatment of various antidepressants on blood glucose level and duration of immobility in euglycemic condition in tail suspension test using mice

Treatment (mg/kg)	Difference in blood glucose level (mg/dl)		Duration of immobility (sec) 40 min after treatment	
	Acute	Chronic	Acute	Chronic
Vehicle	8.75 ± 3.75	12.12 ± 3.75	192.25 ± 5.0	194.75 ± 2.680
Amitryptiline (10)	83.25 ± 6.78*	71.25 ± 9.59*	144.25 ± 1.10*	138.75 ± 7.34*
Imipramine (10)	35.0 ± 0.80*	20.75 ± 1.02	155.5 ± 5.25*	140.25 ± 3.11*
Fluoxetine (10)	30.33 ± 1.04*	14.5 ± 1.32	163.5 ± 3.70*	155.25 ± 1.70*
Trazodone (10)	34.25 ± 1.10*	- 31.25 ± 4.34*	171.5 ± 3.73*	187.25 ± 1.37
$F_{(4,20)}$	59.25	52.04	20.08	45.72

n = 5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* P < 0.05 as compared with vehicle group.
Correlation between BGL (acute) and duration of immobility = -0.87,
Correlation between BGL (chronic) and duration of immobility = -0.70

In hyperglycemic condition the difference in blood glucose level was found to be 24.5 ± 2.25 mg/dl and total duration of immobility was observed to be 176.25 ± 2.86 sec. Treatment with imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), trazodone (10 mg/kg, i. p.), and fluoxetine (10 mg/kg, i.p.) increased blood glucose level (P<0.05) from the initial level and decreased total duration of immobility (P<0.05) [Table 5]. Correlation coefficient between difference in blood glucose level and duration of immobility was observed to be 0.7.

In hypoglycemic condition, the difference in blood glucose level was observed to be 10.0 ± 0.57 mg/dl and total duration of immobility was observed to be 206.25 ± 3.19 sec. Treatment with imipramine (10 mg/kg, i.p.), amitryptiline (10 mg/kg, i.p.), and trazodone (10 mg/kg, i.p.) resulted in an insignificant increase in blood glucose level from the initial level and resulted in decreased total duration of immobility (P<0.05). Fluoxetine (10 mg/kg, i.p.) increased blood glucose level (P<0.05) from the initial level and decreased total duration of immobility (P<0.05). Correlation coefficient between difference in blood glucose level and duration of immobility was observed to be 0.5 [Table 6].

Table 5: Effect of various antidepressants on blood glucose level and duration of immobility in hyperglycemic condition (pretreatment with 5% Dextrose- 2 gm/kg) in tail suspension test using mice

Treatment (mg/kg)	Difference in blood glucose level (mg/dl)	Duration of immobility (sec) 40 min after treatment
Vehicle	24.5 ± 2.25	176.25 ± 2.86
Amitryptiline (10)	127.5 ± 6.94*	119.0 ± 3.53*
Imipramine (10)	66.0 ± 2.73*	139.75 ± 1.25*
Fluoxetine (10)	57.5 ± 4.94*	140.75 ± 2.95*
Trazodone (10)	49.25 ± 5.73*	143.75 ± 3.44*
$F_{(4,20)}$	62.03	49.54

n=5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* $P < 0.05$ as compared with vehicle group. Correlation = - 0.90

Table 6: Effect of various antidepressants on blood glucose level and duration of immobility in hypoglycemic condition (induced by physiological stress) in tail suspension test using

Treatment (mg/kg)	Difference in blood glucose level (mg/dl)	Duration of immobility (sec) 40 min after treatment
Vehicle	10.0 ± 0.57	206.25 ± 3.19
Amitryptiline (10)	12.5 ± 0.94	117.0 ± 2.53*
Imipramine (10)	11.0 ± 0.73	129.75 ± 1.25*
Fluoxetine (10)	13.0 ± 0.94	143.75 ± 1.95*
Trazodone (10)	11.25 ± 0.73	146.75 ± 2.44*
$F_{(4,20)}$	2.95	210.80

n=5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* $P < 0.05$ as compared with vehicle group.

Reserpine antagonism

In reserpine treated rat the difference in blood glucose level was found to be 9.5 ± 1.32 mg/dl. Treatment with fluoxetine (10 mg/kg, i.p.), imipramine (10 mg/kg, i.p.), trazodone

(10 mg/kg, i.p.), and amitryptiline (10 mg/kg, i.p.) resulted in increased blood glucose level from initial level (P< 0.05) [Table 7]. Treatment with reserpine resulted in fall in rectal temperature whereas fluoxetine (10 mg/kg, i.p.), imipramine (10 mg/kg, i.p.), and amitryptiline (10 mg/kg, i.p.) antagonized reserpine induced hypothermia at 1 h. Imipramine (10 mg/kg, i.p.), and amitryptiline (10 mg/kg, i.p.) antagonized reserpine induced hypothermia at 1.5, 2, 2.5, and 3 h. The effect of reserpine induced hypothermia was not antagonized by trazodone (10 mg/kg, i.p.) [Table 7].

Table 7: Effect of various antidepressants on blood glucose level and rectal temperature (^{0}F) in acute reserpinised rats

Treatment (mg/kg)	Difference in BGL (mg/dl)	Rectal Temperature in ^{O}F (Mean SEM) at					
		0	60	90	120	150	180 min
Reserpine (3)	9.5 ±1.32	98.12 ± 0.47	93.37± 0.63	92.90± 0.30	94.42± 0.19	93.95± 0.27	94.97± 0.37
Amitryptiline (10) + Reserpine (3)	52.75 ± 3.19*	98.92± 1.19	98.32± 1.06#	98.20± 0.54#	100.3± 0.54#	100.4± 0.58#	100.38± 0.50#
Imipramine (10) + Reserpine (3)	28.25 ± 3.34*	98.6 ± 0.50	98.72± 0.46#	98.95± 0.64#	98.92± 0.21#	98.85± 0.43#	99.4± 0.50#
Fluoxetine (10) + Reserpine (3)	35.0 ± 1.22*	98.52± 0.42	98.8± 0.53#	98.75± 0.52	98.37± 0.39	97.95± 0.45	98.25± 0.59
Trazodone (10) + Reserpine (3)	22.75 ± 0.94*	98.12± 0.31	94.0± 0.45	93.75± 0.77	94.42± 0.52	96.55± 0.25	98.77± 0.59

n=5, observations are mean ± SEM (ANOVA followed by Dunnett's test).* P < 0.05 as compared with reserpine group. # P < 0.05, analysed by Kruskal wallis test followed by Dunns test. BGL- blood glucose level, RT- rectal temperature

Discussion

It is known that antidepressants increase synaptic levels of noradrenaline (NA), serotonin (5-HT) and in some cases dopamine by inhibiting the reuptake of monoamine at the presynaptic terminals resulting in elevation of catecholamine extracellularly. Many antidepressants, which potentiate the action of catecholamine can cause hyperglycemia by action through α adrenoceptors (by inhibition of insulin secretion from β cell pancreas and reduction of glucose uptake by adipose tissues and muscles) and β adrenoceptors (by enhancing glycogenolysis and gluconeogenesis in liver and glycogen secretion from cells of islets of Langerhans)(21). Amitriptyline is known to potentiate amine mediated synaptic transmission in the central nervous system by blocking reuptake of noradrenaline and dopamine (22). Our observations are in congruence with those of Trulson and Himelii (23), who observed increased levels of noradrenaline in streptozotocin diabetic rats.

As the turnover rate of monoamine is decreased in diabetic rats (24), the effect of antidepressants was studied in mice treated with alloxan. Acute treatment with various antidepressant drugs has resulted in significant increase in blood glucose level and a significant decrease in the total duration of immobility in forced swim test and tail suspension test. Amitriptyline produced a more prominent increase in blood glucose level due to its potent reuptake inhibitory properties of NA and 5-HT at nerve endings (25) and a weak dopamine blocking effect (26). Fluoxetine, a selective serotonin reuptake inhibitor increased blood glucose level and total duration of immobility was reduced. Cryan *et al.,* (27) have suggested that activation of 5-HT_{2C} receptor may be responsible for imparting the antidepressant property of fluoxetine and other antidepressants. Trazodone, an atypical antidepressant is a 5-HT_2 receptor antagonist and has weak 5-HT uptake inhibitory properties. It is metabolized to *m*- chlorophenylpiperazine (m-cpp) which is a 5-$HT_{1A,}$ 5-$HT_{1B,}$ 5-HT $_{1C}$ agonist as well as 5-$HT_{2A/2C}$ agonist (28). It is reported that m-CPP dose dependently increases plasma glucagon level which is mediated by 5-$HT_{2A/2B}$ receptors, which in turn facilitates adrenaline release (29).

Chronic treatment with tricyclic antidepressants increased blood glucose level which was less prominent as compared to their acute treatment because long term administration of antidepressant results in desensitization of presynaptic α_2 receptor (30) as activation of α_2 receptor reduces adenylate cyclase in islet homogenate and α agonist lowers c-AMP in intact islet cells resulting in inhibition of insulin release (31). The decrease in total duration of immobility is due to the fact that repeated administration of tricyclic antidepressant drug reduces mice immobility in forced swim test by a mechanism which seems to involve down regulation of β and presynaptic α adrenoceptors (32). An overall increase of serotonergic neurotransmission caused by desensitization of 5-HT_{1A} autoreceptors in serotonergic dorsal raphe complex may be involved which justifies the observations of chronic treatment of fluoxetine. Chronic administration of trazodone showed a significant decrease in blood glucose level which may be related to the down regulation of 5-HT_{1A} receptors which is involved in blood glucose regulation (6).

In hyperglycemic condition induced by dextrose in our study, counter-regulatory hormone, insulin, may be released but antidepressant drugs increase blood glucose by increasing sympathetic transmission and rendering insulin less effective (33). In hypoglycemic condition (induced by swim test in our study), the sensitivity to the effect of insulin is enhanced after physical exercise (34). The counter regulatory hormones adrenaline, glucagon, growth hormone are released which may increase glucose output as observed with antidepressants. Alloxan in combination with antidepressants increased blood glucose level and total duration of immobility decreased in comparison to antidepressant treatment when given alone. This observation is similar to the findings of Sevak et al., (13) who observed that haloperidol is less potent to produce catalepsy in diabetic rats is consistent with reports of altered dopamine receptor binding in diabetes. Reserpine by depleting NA and 5-HT stores induces hypothermia (35). Depletion of NA and 5-HT is expected to modulate glucose homeostasis. Antidepressants antagonize the effect of reserpine and may also affect glucose regulation. In our study all the selected antidepressant drugs except trazodone antagonized reserpine induced hypothermia. Thus, in conclusion, the study reveals a good correlation between blood glucose level and antidepressant activity amongst various marketed antidepressants.

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