Modulation of conditioned avoidance response and quetiapine-induced metabolic syndrome by rosuvastatin and CDP-choline in rats

Sir,

Metabolic syndrome diabetes mellitus, lipid abnormalities, and weight gain have increasingly been recognized with the use of the newer, atypical antipsychotic drugs like quetiapine**.** The prevalence of metabolic syndrome in these studies was around 40%.[1,2] Physical disorders such as obesity, hyperlipidemia, hypertension, and type-2 diabetes mellitus are becoming recognized as significant comorbidities in patients with bipolar disorder (BD).[3] Atypical antipsychotics are one of the important treatment options for bipolar patients who are manic and/or psychotic. However, in recent years, there has been growing concern about the potential metabolic

side effects of antipsychotics.[4,5] In this regards study was conducted to find out the effect on glucose, serum triglyceride, and liver glycogen with combination of quetiapine (QT) with rosuvastatin (RS) and QT with cytidine diphosphate-choline (CDC) in CAR-induced rats.

The rats (Wistar rat) were divided into nine groups, each group containing eight rats. In this study, psychotic symptoms were induced in rats through Conditioned Avoidance Response (CAR) using Cook's pole climbing apparatus. After the induction of CAR training of animal for 7 days, drug treatment was given for 21 days [Table 1]. On 22nd day under light anesthesia 1 ml of blood was collected through retro-orbital sinus[6] for estimation of blood glucose and triglyceride level and then the animals were sacrificed to determine the liver glycogen concentration. This study was approved by the Institutional Animal Ethics Committee, Jamia Hamdard, New Delhi. Statistical analysis used mean ± SEM, analysis of variance (ANOVA), followed by Dunnett's *t*-test. Values were considered statistically significant, when $P < 0.05$.

Effect of quetiapine, rosuvastatin, and CDP-choline alone and in combination on blood glucose, triglyceride, and liver glycogen in CAR-induced rats were presented in Table 2. The normal blood glucose level was found to be 79.19 mg%.

Table 1: Treatment schedule

Group (*n*=8)	Drug treatment	Dosage route of administration (p.o.)
I	Normal saline (vehicle)	1 ml/kg
II	0.5% CMC	1 ml/kg
III	Quetiapine	30 (mg/kg)
IV	Rosuvastatin	10 (mg/kg)
V	Rosuvastatin	20 (mg/kg)
VI	CDP-choline	100 (mg/kg)
VII	Quetiapine+rosuvastatin	30+10 (mg/kg)
VIII	Quetiapine+rosuvastatin	30+20 (mg/kg)
IX	Quetiapine+CDP-choline	30+100 (mg/kg)

Treatment duration=21 days (drug treatments were given to all groups after the induction of conditioned avoidance response)

There was an increase in the blood glucose levels of rats exposed to CAR (group II) ($P < 0.05$). Quetiapine (30 mg/kg p.o. for 21 days) produced a significant ($P < 0.01$) rise in the blood glucose level in the CAR-induced rats (group III) when compared with normal control (group I) and pathogenic control (group II). Rosuvastatin (10 and 20 mg/kg p.o.) and CDP-choline (100 mg/kg p.o.) did not affect the blood glucose levels (groups IV, V, and VI). Rosuvastatin 10 and 20 mg/kg p.o. and CDP-choline 100 mg/kg p.o. produced significant ($P < 0.01$) reduction of quetiapine induced rise in blood glucose levels (groups VII, VIII, and IX).

The normal triglyceride level was found to be 70.99 mg%. There was an increase in the triglyceride levels of rats exposed to CAR (group II) ($P < 0.05$). Rosuvastatin and CDP-choline did not produce significant changes in the levels of triglycerides in CAR-induced rats (groups IV, V, and VI). However, rosuvastatin and CDP-choline produced significant ($P < 0.01$) reduction of quetiapine induced rise in serum triglycerides levels (groups VII, VIII, and IX).

After induction of CAR for 7 days in rats, no significant ($P > 0.05$) change in the liver glycogen level was observed when compared with the vehicle control group. Treatment with quetiapine (30 mg/kg, group III) resulted in a no significant ($P > 0.05$) change in the liver glycogen levels compared to the normal control (group I) and pathogenic control (group II). Rosuvastatin 10 and 20 mg/kg p.o. caused reduction in liver glycogen levels (groups IV and V). CDP-choline 100 mg/kg p.o. had no significant effect on the level of liver glycogen in CAR-induced rats (group VI). Rosuvastatin and CDP-choline did not produce significant changes in the levels of liver glycogen in CAR-induced rats (groups VII, VIII, and IX).

In the present study, it was observed that after induction of CAR in rats for 21 days, the fasting glucose and triglyceride level were considerably increased as compared to normal rats, suggesting that induction of CAR itself can lead to metabolic

Table 2: Effect of quetiapine, rosuvastatin, and quetiapine with CDP-choline alone and in combination on different parameters in CAR-induced rats

Group (*n*=8)	Treatment	Dose (p.o.) mg/kg	Glucose levels (mg %)	Triglyceride level (mg%)	Liver glycogen mg/500 mg liver tissue
I	NS	1 ml/kg	79.19±1.44	70.99±4.60	83.31±4.27
II	CAR+0.5% CMC	1 ml/kg	95.73±5.16*	85.48±4.16*	86.42±3.71
III	CAR+QT	30	184.78±2.36$^{**, \#\#}$	149.86±2.44$^{**, \#\#}$	90.95±2.90
IV	CAR+RS	10	83.45±2.00	63.34±1.76	69.34±1.45$^{*, \#\#, \dagger\dagger}$
V	CAR+RS	20	74.34±3.13	58.32±4.68	64.08±1.41$^{**, \#\#, \dagger\dagger}$
VI	CAR+CDC	100	77.37±3.48	75.72±2.35	81.97±4.38
VII	CAR+QT+RS	30+10	118.39±3.91$^{**, \#\#}$	117.76±3.70††	74.22±2.17
VIII	CAR+QT+RS	30+20	84.08±5.02††	71.74±4.56††	81.18±2.56
IX	CAR+QT+CDC	30+100	111.84±7.26††	78.22±4.18††	78.34±5.06

CAR=Conditioned avoidance response; QT=Quetiapine; RS=Rosuvastatin and CDC=Cuetiapine with CDP. Values are mean±SEM (*n*=8). $^{*}P<0.05$ compare with NS, $^{**}P<0.01$ compare with group I, $^{\#\#}P<0.01$ compare with group II, $^{\dagger\dagger}P<0.01$ compare with group III. (ANOVA followed by Dunnett's *t*-test)

syndrome. Similar observation was reported earlier.[7] There was a significant rise in blood glucose level in rats treated with quetiapine, 30 mg/kg (group III). This rise in blood glucose and triglyceride level in this group III implies that quetiapine aggravate the metabolic syndrome induced by CAR. The nonsignificant per se effect of rosuvastatin (10 and 20 mg/kg) and CDP-choline (100 mg/kg) on glucose level of CAR-induced rats reveals that rosuvastatin and CDP-choline did not aggravate metabolic syndrome. However, the reduction of quetiapine induced rise in glucose and TG levels by rosuvastatin and CDP-choline reveals that these drugs could attenuate the metabolic syndrome caused by quetiapine. The nonsignificant changes in the liver glycogen level of CAR-induced rats and quetiapine-treated rats indicate that liver plays a minor role in the metabolic syndrome caused by CAR or quetiapine. The reduction of glycogen levels caused by rosuvastatin reveals that statins have mild adverse affect on liver glycogen storage capacity. However, the nonsignificant effect of CDP-choline on liver glycogen reveals that CDP-choline did not produce adverse effects on liver function. The nonsignificant effects of rosuvastatin and CDP-choline on liver glycogen levels of quetiapine-treated CAR-induced rats further confirm that these two drugs attenuate. Study concluded that rosuvastatin and CDP-choline could decrease the metabolic syndrome caused by quetiapine and CAR. It was observed that after induction of CAR in rats for 7 days, the fasting glucose level was considerably increased as compared to fasting blood glucose level of normal rats, suggesting that schizophrenia itself can lead to glucose imbalance.

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