Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst088P.pdf

Attenuation Of High Fat Diet And Clozapine-Induced Weight Gain, Impaired Glucose Metabolism And Cataleptogenic Effects In Rats Treated With Berberine

Among atypical antipsychotics, clozapine ranks highest in terms of the risk for weight gain and developing diabetes and/ or exacerbation of existing type2 diabetes(1). High fat diet-induced weight gain may be the most noticeable signal of Metabolic syndrome and the most distressing issue among diabetic patients (2). Berberine is a chemical found in plants including *European barberry* and *Berberis vulgaris* and seems to slightly reduce blood sugar level in diabetic patientsas effectively as metformin and rosiglitazone (3). The aim of this investigation was to determine the mechanistic part of berberine to attenuate high-fat-diet and clozapine-induced weight gain and impaired glucose tolerance (a pre diabetic state) in rats.

Twenty four age and weight matched adult, female Albino wistar rats (Dow University of Health Sciences, Pakistan), weighing 200$\pm$50gm at the start of the study were pair housed (in cages measuring 30 x 59 x 24cm). The rats were maintained under standard laboratory conditions on a 12 hour light-12hour dark cycle (lights on at 7:00 am) in a temperature controlled room at 21$\pm$2 ºC and humidity of 40-50%. All experiments were carried out in strict accordance with the Guide for the Care and Use of Laboratory Animals (Institutional Animal Ethical Committee; IAEC University of Karachi, Pakistan). Rats were randomly assigned to two groups fed on (i) Normal lab chow (n=12) and (ii) High Fat diet (n=12) for four weeks. Food Intake and Body weight data were monitored weekly. Blood glucose levels were obtained by pricking the tail vein using glucometer at time 0, 30, 60, 90, 150 minutes on 4^{th} week. Followed by the significant development of obesity and state of hyperglycemia, rats were further sub-divided into four groups (n=6 in each group) at the end of 4^{th} week of study. Clozapine ($10mg.kg^{-1}$) and berberine ($500mg.kg^{-1}$) were injected daily (between 9:00 to 10:00 A.M single injection/2 weeks) to all groups. Controls received an equal volume of Saline (0.9% NaCl) ($1.0mg.ml^{-1}.kg^{-1}$i.p.). Behavioural testing was done using bar test (cataleptogenic effects of a drug) and open field arena to determine the antipsychotic-like profile of berberine and clozapine. Data were presented as Means$\pm$SEM (n=24). Statistical significance was tested using one- or two-way Analysis of Variance (ANOVA) followed by Newman keuls *Post hoc* test by Graph Pad Prism (6.0) software support.

Impaired glucose metabolism and obesity have been shown to be constituents of the metabolic syndrome. The present data suggest that clozapine may be more likely to cause adverse metabolic effects in High fat diet fed rats when compared with rats injected with berberine. Blood glucose levels were significantly ($p<0.01$) higher in rats fed on High fat diet and clozapine ($10mg.kg^{-1}$), and this can be explainable in terms of progression of insulin resistance that may cause diabetes. Behavioural data revealed that berberine ($500mg.kg^{-1}$) exhibited a significant ($p<0.05$) antipsychotic-like profile in bar test while significant ($p<0.05$) increases were observed in exploratory activity in high fat fed rats. Berberine-induced reduction in body weights was significant ($p<0.01$) and in time-dependent manner in last two weeks primarily in high fat fed rats. Significant ($p<0.01$) decreases in Food intake can be possibly related to serotonergic interaction of berberinevia activation of 5HT1A auto receptors and inhibition of postsynaptic 5-HT1A and 2C receptors which are largely involved in appetite regulation. It is concluded that clozapine impairs glucose metabolism and appetite-regulating system while berberine demonstrated more effective at regulating appetite and controlling body weight.

(1) Peng WH *et al.* (2004). *Life Sci* **75**: 2451-2462.

(2) Yueshan Hu *et al.* (2014) *Plos One* **9**: e93310.

(3) Jun Yin *et al.* (2012). *ActaPharmaceuticaSinica B* **2**: 327-334.