Olanzapine inhibits glycogen synthase kinase-3β: An investigation by docking simulation and experimental validation.

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Olanzapine was investigated as an inhibitor of glycogen synthase kinase-3β(GSK-3β) in an attempt to evaluate its effect on blood glucose level. The investigation included simulated docking experiments to fit olanzapine within the binding pocket of GSK-3βfollowed by in vitro enzyme inhibition assay as well as in vivo subchronic animal treatment. Olanzapine was found to readily fit within the binding pocket of GSK-3βin a low energy orientation characterized with optimal attractive interactions bridging the tricyclic thienobenzodiazepine nitrogen and sulfur atoms of olanzapine and the residue of VAL-135 of GSK-3β. In vivo experiments showed a significant decrease in fasting blood glucose level in Balb/cmice at 1.0, 2.0 and 3.0 mg/kg dose levels (Pb0.05) and 6 fold increase in liver glycogen level at the 3 mg/kg dose level (Pb0.001). Moreover; olanzapine was found to potently inhibit recombinant GSK-3βin vitro (IC50value=91.0 nM). Our findings strongly suggest that olanzapine has significant GSK-3βinhibition activity that could justify some of its pharmacological effects and glucose metabolic disturbances.