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Olanzapine causes beta-cell dysfunction and apoptosis via mitochondrial pathway

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Olanzapine, a commonly used atypical antipsychotic drug, is known to induce diabetes and diabetes-associated heart disease. However, the associated mechanisms are not well elucidated. Olanzapine-caused insulin resistance directly or through obesity could be a reason. However this can't explain the acute effect of olanzapine i.e. hyperglycaemic emergencies (hyperglycaemia, diabetic ketoacidosis, hyperosmolar hyperglycaemic state). We propose that olanzapine-induced direct damage on beta-cells may play a key role in olanzapine-induced diabetes. In this study, we examined the effects of olanzapine on beta-cell survival ability and mitochondrial apoptotic pathway. Mouse beta-cell line MIN6 was cultured in DMEM medium containing 4.5 g/L D-glucose, supplemented with 50 μM β-mercaptoethanol, 10% fetal bovine serum and 1% Penicillin-Streptomycin and maintained at 37°C incubator with 5% CO2. Cell viability was detected by MTT assay. Apoptosis was determined by BD PharmingemTM Annexin V apoptosis kit I. Mitochondrial functions were measured by Rhodamine assay and ATP production. Key signalling molecules in mitochondrial apoptotic pathway were detected by Western Blotting. Olanzapine decreased the viability of MIN6 cells in a dose- and time-dependent fashion. The olanzapine-induced beta-cell damage was also demonstrated by apoptotic assay. Olanzapine reduced rhodamine retention and ATP production, indicating it damaged beta-cell mitochondria. Western blotting showed that olanzapine decreased mitochondrial anti-apoptotic protein Bcl-2 and increased cleaved caspase 3. In conclusion, olanzapine decreases beta-cell function and viability through mitochondrial pathway. Olanzapine-caused beta-cell damage could explain the acute hyperglycaemic emergencies in humans as well as low compensatory ability to secret more insulin in animal experiments.

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