Summary

Drug-fatty acids conjugates in Diabetes treatment: Role of chain length and degree of unsaturation of fatty acids

Type 1 diabetes (T1D) is a chronic autoimmune disease that results in the loss of insulin producing beta cells within pancreatic islets and due to this proinflammatory cytokine-mediated β-cells dysfunction, chronic complications like kidney failure and other major complications can occur. An urgent screening of small molecules and designing of a proper therapeutic molecule to prevent beta cells destruction is needed as insulin is the only choice of treatment at present. Therefore, Lisofylline (LSF) bearing significant clinical utility in preventing both T1DM and T2DM by suppressing autoimmunity and retaining insulin secretory function of β-cells in the presence of inflammatory cytokines has been selected for this work. However, its hydrophilicity, short half-life and rapid metabolism make it a very challenging molecule to deliver.

In this study, drug-fatty acid prodrugs were synthesized, characterized and evaluated for their anti-diabetic efficacy both in vitro and in vivo. Different categories of FAs (linoleic acid, oleic acid, palmitic acid and α-lipoic acid) were selected based on their chain length and degree of unsaturation and conjugated with LSF to improve its half-life (from 0.7 h to 4h) and to prevent its *in vivo* rapid metabolism. The *in house* synthesized LSF (purity >98%) and all the LSF-fatty acids prodrugs (purity >95%) were characterised by NMR, HR-MS, FTIR and purity by HPLC. The hydrophobicity of the synthesized LSF-fatty acid prodrugs increased with increase in the carbon chain length of fatty acids and also exhibited self-assembling into micelles (70-170 nm). The prodrugs were hemocompatible and non-cytotoxic to mouse insulinoma cells (MIN-6) cells. The micelles exhibited higher cellular internalization compared to free LSF because of hydrophobicity increment in the prodrugs and preserved MIN-6 cells viability under the inflammatory conditions. Prodrugs demonstrated prolonged *in vitro* drug release for 72 h in rat plasma and *in vivo* pharmacokinetic revealed 2-6 folds higher half-life. In streptozotocin induced diabetic animals, prodrugs maintained the blood glucose level throughout 5 weeks of study with a significant increase in insulin level, considerable restoration of the biochemical parameters and preservation of β-cells integrity.

The study confirms successful conjugation of LSF with different FAs exhibiting improved in vitro and in vivo performance than the free drug. We conclude that chain length and double bond in fatty acids influenced pharmacokinetic behaviour and in vivo efficacy of prodrugs with LSF-OA showing the most efficacious anti-diabetic activity.

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