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TR-013A, aselective 11 beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor ameliorates the progression of diabetic cardiomyopathy in mice

Background: High levels of cortisol in humans cause metabolic abnormalities such as insulin resistance, dyslipidaemia etc.,which may lead to diabetic cardiomyopathy (DCM) in type 2 diabetes mellitus (T2DM).11beta-hydroxysteroid dehydrogenase type1 (11β-HSD1) is an enzyme which is responsible for conversion of cortisone to cortisol. Therefore, selective inhibition of 11β-HSD1 activity could offer a new approach to treat complications of T2DM.

Objective: To evaluate the efficacy of selective 11β-HSD1 inhibitor (TR-013A) in attenuating DCM in type 2 diabetic mice.

Methodology: DCM was elicited in C57BL/6J mice by feeding them with high fat diet (HFD) and intraperitoneal injection of streptozotocin at a dose of 75 mg/kg body weight once a day for three days. Mice received only chow diet served as normal control (Group I). The diabetic mice were randomly divided into three groups. Diabetic control (Group II) received vehicle (1% CMC *p.o.*); treatment (Group III) received TR-013A (30mg/kg *bid, p.o*) and standard (Groupd IV) receieved (RU38486 10mg/kg *bid, p.o*) for 21 days. Blood glucose was monitored at specific time interval during the study period.

Result & Discussion: TR-013A has significantly lowered plasma glucose level, lipid parameters compared to the diabetic control group. The plasma glucose lowering effect was comparable to that of RU38486. Furthermore, cardiac remodeling events such as inflammation, fibrosis, hypertrophy and oxidative stress were reversed by both TR-013A and RU38486 in comparison to diabetic control. Interestingly, the mice did not gain weight upon treatment with TR-013A.

Conclusion: These results demonstrate that TR-013A does exhibit anti-hyperglycaemic, anti-lipidaemic, anti-hypertrophic, anti-oxidative, anti-inflammatory and anti-fibrotic activities. Thus, inhibition of 11β-HSD1 can be an attractive therapeutic target for DCM.

Biography

Punniyakoti V Thanikachalam obtained his PhD from Niigata University of Pharmacy and Applied Life Sciences, Niigata, Japan. He is a Recipient of prestigious JSPS Scholarship for Postdoctoral studies in Osaka University, Japan. He has published more than 50 papers in ISI journals with cumulative impact factor of 165. His particular area of interest in research is to discover novel molecules for the treatment of cardiovascular diseases.At present, he is associated with International Medical University, Kuala Lumpur, Malaysia.

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