Abstract

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Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from defective insulin secretion due to β-cell specific autoimmune process (type 1 diabetes – T1D) and/or increased cellular resistance to insulin (type 2 diabetes – T2D). In T2D, glucose levels and free fatty acids in the blood increase and their heightened levels in due course of time induce chronic oxidative stress and stimulate pro-inflammatory cytokines' production (leptin, resistin, TNF-α, etc.), ultimately leading to pancreatic β-cell loss and chronic hyperglycemia. Loss of functional β-cell mass is a critical factor in the pathogenesis of T1D and T2D, eventually resulting in chronic hyperglycemia. Therefore, it is essential to develop therapies that prevent or even reverse the deterioration of β-cell function. Thus, the study was aimed to investigate the therapeutic potential of melatonin in combination with GABA on β-cell regeneration in streptozotocin (STZ)-induced T1D and on a high-fat diet (HFD)-induced T2D mouse models. Additionally, the study aimed to investigate leptin (*LEP*) and its receptor's (*LEPR*) genetic variants and their transcript levels in peripheral blood mononuclear cells (PBMCs), their protein levels in plasma, and genotype-phenotype correlation with various metabolic parameters and T2D susceptibility in Gujarat population.

Our *in vivo* studies suggest that monotherapies and combination therapy significantly reduced FBG levels (M, $p<0.001$; G, $p<0.001$; M+G, $p<0.001$) by increasing plasma insulin levels (M, $p<0.01$; G, $p<0.001$; M+G, $p<0.001$) with a consequent increase in glucose tolerance (M, $p<0.001$; G, $p<0.001$; M+G, $p<0.001$) in STZ-induced T1D mouse model by inducing β-cell proliferation (M, $p<0.01$; G, $p<0.01$, M+G, $p<0.001$) and trans-differentiation (S, $p<0.05$; M, $p>0.05$; S+M, $p<0.05$) besides reducing β-cell apoptosis (M, $p<0.01$; G, $p<0.05$, M+G, $p<0.01$). Furthermore, monotherapies were as efficacious as combination therapy in the amelioration of HFD-induced T2D manifestations by improving metabolic profile (M, G, $p<0.01$; M+G, $p<0.001$), glucose and lipid metabolism (M, G, $p<0.01$; M+G, $p<0.001$), increasing β-cell mass and islet number (M, G, M+G, $p<0.001$), increasing insulin and leptin sensitivity (M, M+G, $p<0.001$; G, $p<0.01$) in the peripheral tissues, and elevating mitochondrial biogenesis (M, M+G, $p<0.001$; G, $p<0.01$) and respiration (M, G, $p<0.05$; M+G, $p<0.01$). Our findings on genetic association study revealed that the GG genotype of *LEPR rs1137101 A/G* polymorphism was associated with increased FBG ($p=0.027$) and TC ($p=0.025$) levels, along with elevated leptin ($p<0.0001$) and decreased sOb-R ($p=0.0294$) protein levels, which could pose an increased risk towards T2D susceptibility in Gujarat population.

Thus, the research findings conclude that melatonin and GABA monotherapies are as effective as the combination therapy in ameliorating T1D and T2D manifestations in experimental diabetic mouse models. Overall, this knowledge can eventually be used in future translational research leading to the development of targeted drug therapy for diabetes. Further, to explore the therapeutic potential of melatonin in combination with GABA in clinical studies, it is essential to consider the duration and dosage of melatonin besides the relative timing of its intake, concerning the glycemic challenge. Additionally, the findings open new avenues in understanding the role of *LEP* and *LEPR* (along with genetic variants) in obesity and leptin resistance-induced T2D in Gujarat population.