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Pharmacological Modulation of Endo cannabinoid System in Pancreatic Islets, a Different Strategy for Prediabetes and Diabetes Treatment

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Abstract

Rimonabant was developed as a therapeutic option for obesity and diabetes. However, it was retired after clinical reports of secondary effects. Previously we evaluated the effects of a novel synthetic analogue denominated BAR-1 in gene expression and insulin secretion from isolated rat islets. In our recent study we investigated effects of BAR-1 administration on mice models of prediabetes and diabetes, with specific interest in pancreatic islets. CD-1 mice fed with hypercaloric diet or diabetes-induced with streptozoticin and were treated with 10 mg BAR-1 or vehicle for 4 and 8 weeks. Body weight and mass, oral glucose tolerance test, triglycerides, HbA1c, and insulin in serum were measured, whole fixed pancreas were analysed by histology, and gene expression, insulin and glucagon secretion, were evaluated in isolated islets. BAR-1 controlled weight gain for the first 4 weeks in prediabetic mice. HOMA index presented a significant decrease in treated mice, and reduction in the area under the curve of the oral glucose test. In isolated islets glucose-stimulated insulin secretion was increased, gene expression in islets was modified after 4 weeks of BAR-1 administration. In diabetic mice, BAR-1 presented a partial recovery of islet integrity, with positive insulin and glucagon expression. In silico modelling suggest a direct interaction with CB1 receptor. In conclusion, BAR-1 treatment provides a short improvement in prediabetic and diabetic animal models, modulating pancreatic islets physiology, and probably, metabolic adaptations in other organs.

Keywords: Endocannabinoid system; CB1 receptor antagonist; Pancreatic islets; Diabetes animal model

Introduction

The endocannabinoid receptors and their regulatory functions in many organs, including pancreatic islets, have been studied in the context of diabetes since 2006 [1-5]. Many evidences expose a close relationship between CB1 receptor (CB1r) with islet features such as glucose-regulated insulin and glucagon secretions, cell structure, gene expression, and suggest an active role in the development of diabetes under over-activation. Rimonabant was a synthetic CB1r antagonist tested as obesity and type 2 diabetes treatments, with beneficial effects in different organs, [6-11] but also negative side-effects, including depression [12]. After these, new analogue options have been studied in diabetic animal models and isolated islets [13-15]. Briefly in a previous report we introduced BAR-1, a novel rimonabant-related analog with different CB1r affinity [15]. In isolated pancreatic islets from rat BAR-1 exposure modified gene expression, glucose-stimulated insulin secretion and content. Our next step, recently reported, we evaluated the therapeutic effects of BAR-1 in prediabetic and diabetic mice [16].

Discussion

BAR-1 treatment at 10 mg/kg dose slowed down weight gain in prediabetic mice, induced by hypercaloric diet, with a small difference in size and body mass index. In the same group, glucose-stimulated insulin secretion was increased in isolated islets, without effects in glucose oral test either blood triglycerides. In diabetic-induced mice, BAR-1 administration reduced the area under the curve of oral-glucose tolerance. We assume that CB1r activity is modified within the first month, but overturn by the metabolic alterations in the next weeks. BAR-1 treatment could induce a long-term adaptation of the endocannabinoid system, involved in islet dysfunction. Beside, considering the presence and activity of the endocannabinoid system in nervous system,

adipose tissue and liver, it is possible a complex interaction of BAR-1 with the pancreatic islets function. An interesting effect of BAR-1 was the partial recovery of islet area and morphology observed in pancreas from STZ-induced diabetic animals. Islets presented cells with insulin immunoreactivity, and increased glucagon presence. These results support the relevant role of CB1r activity in preservation of islet integrity, previously reported [17,18]. Consistent with our previous data, glucose-stimulated insulin secretion and insulin expression are enhanced by BAR-1 treatment in islets from prediabetic mice, but these effects decreased after 8 weeks. Glucagon secretion was not modified, but preproglucagon mRNA was reduced in mice under hypercaloric diet. In isolated islets treated with BAR-1 changes in CB1 and CB2 receptors expression were observed. In prediabetic and diabetic mice with BAR-1 administration increased CB1r expression, but not CB2r. Finally we performed the binding interactions of BAR-1 with CB1r, showing the same pattern very similar to reference drugs AM6538, rimonabant and otenabant; the modification of an aromatic ring in BAR-1 increases its hydrophobic interactions, and therefore, the affinity for CB1r; however, it is possible the simultaneous activation of CB2 or GRP55 receptors, as either agonist or antagonist effects.

Conclusion

Our novel analogue BAR-1 is suggested as an optional treatment for prediabetes and diabetes through modulation of the endocannabonoid system. In forthcoming studies, we will explore different doses and administration protocols, focusing on the possible interactions with CB1r in other organs.

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