Journal of the Endocrine Society
AN OPEN ACCESS PUBLICATION

Volume 3, Issue Supplement_1
April-May 2019

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JOURNAL ARTICLE

SAT-165 Does Oligodeoxynucleotide IMT504 Have Any Effect On Beta Cells? A Preliminary Study On MIN6B1 Cell Line

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Journal of the Endocrine Society, Volume 3, Issue Supplement_1, April-May 2019, SAT-165, https://doi.org/10.1210/js.2019-SAT-165
Published: 30 April 2019

Abstract

We have previously demonstrated that treatment with IMT504 promotes significant improvement in the diabetic condition in diverse animal models. We have also shown effects on gene expression on freshly isolated islets from diabetic IMT504-treated animals. Based on these results, here we evaluated if the effects of IMT504 observed *in vivo* were due to direct effects on beta cells. In particular we studied cell viability, enzyme activation and gene expression. A murine beta cell line (MIN6B1) was used. Cells were cultured in DMEM with 20 mM glucose, 15% SFB, 71 uM βmercaptoethanol. Cell viability was analized by MTS: cells were stimulated for 24 or 48 h with 0 (C), 2 (IMT2), 4 (IMT4) and 8 ug/ml (IMT8) of IMT504 in DMEM, 20 mM glucose, 2% SFB, 71 uM βmercaptoethanol. Gene expression of *Pdx1*, *Ins2*, *Ins1* and *Mafa* was analized by qPCR, using cyclophilin as housekeeping gene. Phosphorylation of proteins of interest was analyzed by Western Blot. Cells were stimulated for 24 and 48 h with IMT504 in DMEM, 20 mM glucose, 0.5% BSA, 71 uM βmercaptoethanol. Enzyme phosphorylaton was also assayed at short time stimulation periods i.e. 0, 5, 15 ,30 and 60 min. For gene expression the dosis of IMT504 used were 0 (C), 0.4 (IMT0.4), 2.2 (IMT2.2) and 4 (IMT4) ug/ml; and for Western Blot were 0 (C), 2 (IMT2), 4 (IMT) and 8 (IMT8) ug/ml. No differences in cell viability were observed at the time points studied (ANOVA for repeated measures: NS). Expression of *Pdx1* and *Ins2* was significantly increased by 48 h stimulation with IMT504 [ANOVA for repeated measures: *Pdx1* (A.U.): C=0.93±0.05;

IMT0.4=0.80±0.06; IMT2.2=1.04±0.09; IMT4=1.37±0.09 $p<0.05$, IMT4 different from C and IMT0.4; *Ins2* (A.U.): C=0.99±0.04; IMT0.4=1.04±0.06; IMT2.2=1.13±0.06; IMT4=1.52±0.08 $p<0.05$, IMT4 different from C and IMT0.4], while no changes in Ins1 and Mafa were observed (NS). $pGSK3_{\beta}/GSK3_{\beta}$ ratio (A.U.) and pAkt/Akt ratio (A.U.) were calculated and informed as fold increase with regard to 0 min. At 60 min, $pGSK3_{\beta}/GSK3_{\beta}$ ratio was increased compared to 0 min (ANOVA with repeated measures: $pGSK3_{\beta}/GSK3_{\beta}$ ratio (A.U.) 0 min=1, 5 min=1.15±0.06, 15 min=1.20±0.05; 30 min=1.54±0.14; 60 min=2.04±0.17, 60 min different from 0 min, $p<0.03$). No significant differences were observed in pAkt/Akt ratio (ANOVA with repeated measures, NS). For 24 and 48 hs we found no significant differences between groups. Our results demonstrate a direct effect of IMT504 on gene expression in beta cells and suggest that IMT504 could exert its actions on beta cells through a pathway that includes $GSK3_{\beta}$ phosphorylation. Further studies must be done to dilucidate their implications on beta cell function recovery in diabetic animals. FUNDING: CONICET, UBA, ANPCYT, FUND. WILLIAMS, FUND. RENÉ BARON, ASOC ORT ARG

Issue Section: Diabetes Mellitus and Glucose Metabolism > Novel Aspects of Diabetes and Metabolic Disease Across Tissues and Developmental Stages