ADENOSINE A\textsubscript{2A} RECEPTOR AGONIST ATL146e IMPROVES ISLET TRANSPLANTATION OUTCOMES IN MICE.

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Introduction: Peri-transplant inflammatory events limit the success of clinical islet transplantation. The effect of the A\textsubscript{2A} adenosine receptor (A\textsubscript{2A}AR) agonist ATL146e on \textit{in vitro} islet function and functional islet graft survival was investigated.

Methods: Islets were isolated from C57BL/6 recipient mice and underwent: 1) glucose-stimulated insulin secretion (GSIS), with or without ATL146e (100nM) in 2hr static incubations using 50 islets/well; or 2) syngeneic islet transplantation (50 islets, renal subcapsular site) in diabetic (IP streptozotocin, 18mg/kg) C57BL/6 recipient mice. In transplant recipients ATL146e (60 ng/kg/min) was administered by mini-osmotic pump beginning 2 days pre-transplant.

Results: Glucose-stimulated insulin secretion from ATL-treated islets demonstrated a stimulation index (SI) significantly less than that observed for vehicle-treated islets (3.75\pm0.45 for islets alone vs. 2.36\pm0.22 for islets + ATL, p<0.01). Decreased SIs in ATL146e-treated islets resulted from increased (1.79\pm0.20, n=9, p<0.05) basal insulin secretion. Islets co-cultured with neutrophils demonstrated a significant reduction in glucose-stimulated insulin secretion, however, culture with ATL146e abrogated this effect (SI=1.41\pm0.17 for islets + neutrophils vs. 2.57\pm0.18 for + with neutrophils + ATL146e, p<0.05). Addition of an ATL146e antagonist (SCH58261) reverse ATL146e’s effect on islet/neutrophil co-cultures (SI=2.59\pm0.31 for islets + neutrophils + ATL146e vs. 1.11\pm0.42 for islets + neutrophils + ATL146e + SCH58261, p<0.05). Further, islets co-cultured with A\textsubscript{2A}AR knock-out neutrophils showed no improvement in GSIS upon addition of ATL146e (SI=1.24\pm0.40 for islets + KO neutrophils vs. 0.90\pm0.10 for islets + KO neutrophils + ATL146e, p<0.05). \textit{In vivo}, diabetic mice receiving vehicle or ATL146e alone did not achieve normoglycemia (n=5,8; >30days). Recipients grafted with 50 syngeneic islets (n=10) achieved normoglycemia within 30 days (20.6\pm3.5 days). ATL146e therapy enhanced the return to normoglycemia (9.9\pm2.9 days, n=7, p<0.031). Transplantation of syngeneic islets to C57BL/6 A\textsubscript{2A}AR-KO recipients treated with ATL146e showed no improvement in functional graft success over controls.

Conclusions: \textit{In vitro} studies show that ATL146e abrogates the deleterious effects of neutrophils on GSIS, and that this effect is mediated by specific activation of A\textsubscript{2A}ARs on neutrophils. Additionally, ATL146e administration \textit{in vivo} improves islet transplant outcome, with reduced grafted islet mass requirement, and shorter time to hyperglycemic reversal.