Program Number: 4396 **Poster Board Number:** A0267
Presentation Time: 8:30 AM–10:15 AM
A GSK-3b modulator delays photoreceptor cell death and preserves visual function in the *rd10* mouse model of retinitis pigmentosa
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Purpose: Retinitis pigmentosa (RP) is a heterogeneous group of inherited retinal dystrophies that lead to blindness. Photoreceptor cell death, reactive gliosis and retinal inflammation are common features in animal models of the disease. The enzyme Glycogen Synthase Kinase-3 Beta (GSK-3β) is involved in inflammatory processes associated to diverse neurodegenerative pathologies. The aim of our study is to test in the *rd10* mouse whether the GSK-3β inhibitor VP3.15 (a small heterocyclic molecule) is a potential therapeutic treatment for RP.
Methods: *Ex vivo* studies: *rd10* retinas at postnatal day 23 (P23) were placed in organotypic culture and treated with the VP3.15 GSK-3β modulator. Photoreceptor cell death was analyzed TUNEL. *In vivo* studies: VP3.15 was injected intraperitoneally into *rd10* mice from P15 to P45. Visual function was evaluated by ERG recording and retinal structure was visualized by immunohistochemistry in cryosections. The expression of pro-inflammatory genes was analyzed by RT-qPCR.
Results: The GSK-3β inhibitor decreased by 50% photoreceptor cell death *ex vivo.* Moreover, intraperitoneal administration of VP3.15 to *rd10* mice preserved photoreceptor cell number and prevented microglial infiltration at P23, decreased pro-inflammatory TNF-α and IL-1β, as well as GFAP gene expression at P23, and improved visual function up to P46.
Conclusions: GSK-3β inhibitors may constitute a therapeutic strategy for the treatment of Retinitis Pigmentosa.
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Flibanserin, a FDA approved dual serotonin receptor agonist-antagonist, provides retinal neuroprotection from light induced damage
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Purpose: We assessed the neuroprotective effects of Flibanserin (BIMT-17, Addyi), a dual 5-HT_{1A} agonist and 5-HT_{2A} antagonist, in a light-induced retinopathy mouse model.
Methods: Albino BALB/c mice and 5-HT_{1A} KO mice were injected intraperitoneally with either vehicle (to serve as controls) or doses of flibanserin ranging from 0.75 mg/kg to 15 mg/kg. Naïve controls did not receive any injections or light damage. Mice were administered a single injection of flibanserin immediately before light damage or received a five-day treatment course at 48, 24, and 0 hours before light damage and 24 and 48 hours after light damage. Exposing vehicle injected mice to 10,000 lux of uniform light for one hour resulted in light-induced retinopathy. Seven days after light damage, spectral domain optical coherence tomography (SD-OCT) was used to assess retinal structure and electroretinography (ERG) to assess retinal function.
Results: A five-day treatment course of 3 mg/kg, 6 mg/kg, 9 mg/kg and 15 mg/kg flibanserin significantly preserved outer retinal structure and function in a dose dependent manner compared to the vehicle group ($p<0.05$, ANOVA). A single administration of 15 mg/kg flibanserin completely protected mouse retinas from light-induced retinopathy. Outer retinal thickness and function of the 15 mg/kg flibanserin group were not significantly different from the naïve group ($p>0.05$, ANOVA). Interestingly, a single 15 mg/kg dose of flibanserin injected immediately prior to light damage completely protected 5-HT_{1A} KO mouse retinas both structurally and functionally from light-induced retinopathy.
Conclusions: Multiple administrations of flibanserin at doses equal to 3 mg/kg or greater can provide partial neuroprotection, while a dose of 15 mg/kg can provide full neuroprotection. Flibanserin is a fast acting drug that can elicit neuroprotection when delivered immediately before light damage. Dosing 5-HT_{1A} KO mice with 15 mg/kg of flibanserin did not lead to a reduction in neuroprotection, suggesting that flibanserin's neuroprotective effects are not mediated exclusively through 5-HT_{1A}, but potentially through 5-HT_{2A} as well.
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Creatine protects rat retinal neurons in an in vitro model of metabolic compromise
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Purpose: There is increasing interest in creatine as a potential agent to provide neuroprotection. Our study aimed to investigate the effect of prophylactic creatine on cultured retinal cells subjected to mitochondrial electron transport chain inhibition as a model of metabolic and energetic dysfunction.
Methods: Mixed rat retinal cultures comprising neurons and glia were established and treated at six days in vitro with a range of creatine concentrations (no creatine controls, 0.1mM, 0.5mM, 1.0mM, and 5.0mM) for 24 hours. Subsequent to this, half of each group was subjected to a 1-hour or a 24-hour incubation with sodium azide (10mM, N=12; and 1mM, N=4 respectively). Cells were then fixed and processed for immunocytochemistry. Antibodies labelling distinct neuronal populations (Calretinin and GABA) were used for quantification of viable cells in each group. Furthermore, potential mechanisms of protection were also investigated by assessing apoptosis (TUNEL assay) and levels of adenosine triphosphate (ATP). One-way ANOVA followed by Tukey multiple-comparison test was used for statistical analysis.
Results: 1-hour and 24-hour incubations with sodium azide resulted in losses of up to 85% and 98% respectively for both Calretinin-immunoreactive (IR) and GABA-IR neurons. In the 1-hour azide-treated group, prophylactic treatment of creatine at >0.5mM