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Basic Science/Methodology

4053

A TL1 Team Approach to CNS-Localized Delivery of Glial Cell-Derived Neurotrophic Factor for Treatment of Parkinson's Disease*

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OBJECTIVES/GOALS: Develop a strategy to restrict GDNF diffusion at an injected CNS tissue site for dopamine neuron rescue by endowing it with binding affinity for carbohydrates that are abundant on the cell surface and extracellular matrix. METHODS/STUDY POPULATION: GDNF will be fused to galectin-3 (G3), a human protein that binds to β-galactoside residues of cell surface and matrix glycoproteins. We characterized the binding of G3 fusion proteins to various glycoproteins and primary human myeloid cells. We incubated G3 fusions with CNS tissue ex vivo to measure their binding and depth of penetration via diffusion. We next plan to administer GDNF-G3 via CNS intracranial infusion in a murine PD model and then conduct behavioral PD phenotype testing via rotarod and pole descent to compare to non-parkinsonian controls. We will further examine the effects of GDNF-G3 on degeneration using immunohistochemical examination of post-mortem brain tissue. RESULTS/ANTICIPATED RESULTS: Based on results from previous clinical trials of GDNF delivery, we anticipate that a successful intervention using GDNF-G3 will result in rescue of midbrain dopaminergic neurons in a murine PD model. In murine CNS tissue, we observed binding to glycans at the tissue surfaces when incubated with G3 fusion proteins ex vivo, suggesting GDNF-G3 will remain localized to the injection site. Next we will administer GDNF-G3 via CNS intracranial infusion in a murine PD model and assess efficacy by behavior and histopathology. GDNF-G3-mediated dopamine neuron rescue are expected to slow or reverse the progression of PD in these animal models. DISCUSSION/SIGNIFICANCE OF IMPACT: PD treatments focus on symptomatic relief. Standard therapies have not been efficacious in rescuing of dopaminergic neurons. GDNF-G3 administered at the site of neurodegeneration would represent a milestone on the path to treating PD pathology and address limitations of GDNF delivery.

4163

Aging and Smoking Exacerbates Post-Stroke Complement Driven Neuroinflammation

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OBJECTIVES/GOALS: Following stroke, complement-dependent neuroinflammation exacerbates secondary injury and worsens acute and chronic outcomes. We have shown that an injury site-targeted complement inhibitor (B4Crry), that targets specifically to the ischemic brain, inhibits complement activation leading to improved outcomes. Stroke comorbidities have been shown to promote a pro-inflammatory environment in the brain and systemically, and to exacerbate inflammatory responses after injury. We investigated the impact of age and smoking on acute outcomes after stroke and assessed whether increased complement activation contributes to the worsening outcomes with these stroke comorbidities. METHODS/STUDY POPULATION: Mouse brain endothelial cells (bEnd3) were exposed to hypoxia followed by exposure to serum that was derived from either cigarette smoke (CS)-exposed mice or naïve mice, and IgM and C3d deposition assessed. Adult (12 weeks) and aged (1 year) mice were subjected to 1h transient middle cerebral artery occlusion. Animals were exposed to CS for 3-6 months (5hr/day, 5days/week) by burning 3R4F cigarettes using a smoking machine. Animals were treated with B4Crry or vehicle intravenously 2h post-MCAO. Survival analysis and neurological deficit scores were performed up to 7 days. Brains were extracted for histological and molecular analyses. RESULTS/ANTICIPATED RESULTS: Following hypoxia, bEnd3 cells exposed to serum from CS-exposed mice had higher C3d and IgM deposition compared to naïve serum. Older and CS-exposed mice had significantly worse neurological deficits and mortality compared to younger adults post-MCAO. B4Crry reduced mortality and motor deficits in young, old and old+CS mice with a higher effect size in comorbid animals. Age and/or CS exposure resulted in larger infarct volumes, and increased levels of C3d deposition and microglial activation compared to young adults, but aged/CS animals treated with B4Crry fared comparable to young adults. DISCUSSION/SIGNIFICANCE OF IMPACT: The pro-inflammatory effects of aging and smoking contribute to worse stroke outcomes, and these effects can be successfully mitigated by injury site-targeted complement inhibition.

4512

Allopregnanolone Dose Finding for Status Epilepticus Treatment by Pharmacokinetic-Pharmacodynamic Modeling using Quantitative EEG in Dogs

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OBJECTIVES/GOALS: Allopregnanolone (ALLO), a modulator of $GABA_A$ receptors, may be useful as a treatment for human and canine benzodiazepine-refractory status epilepticus (SE). Our objective was to develop a phamacokinetic-pharmacodynamic (PKPD) model relating ALLO plasma concentrations to electroencephalographic (EEG) effects in dogs. METHODS/STUDY POPULATION: Four healthy dogs and one dog with epilepsy that had implanted intracranial electrodes were utilized. ALLO doses ranging from 1-6 mg/kg were administered IV over 5 min. EEG data were collected during four IM doses (1-2 mg/kg). Blood samples were collected up to 6 hr following dosing. ALLO concentrations were measured using

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