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Neurogenesis and Recovery of Visual Function After Blast Exposure

Principal Investigator: LINN, CINDY
Institution Receiving Award: WESTERN MICHIGAN UNIVERSITY
Program: VRP
Proposal Number: VR190034
Award Number: W81XWH-20-1-0921
Funding Mechanism: Investigator-Initiated Research Award - Funding Level 1
Partnering Awards:
Award Amount: $363,530.00

View Technical Abstract

PUBLIC ABSTRACT

Vision loss resulting from blast exposure in combat significantly affects a soldier's quality of life and results in a substantial burden on national healthcare systems. Although regeneration of neural tissue is not typical in adult humans once neuronal damage occurs, the ability to generate new retinal neurons in adults could reverse the effects of vision loss. In previous studies from this lab, eye drop application of a specific acetylcholine agonist, PNU-282987, in adult rats and mice triggered robust growth of new neurons in all retinal cell layers in control untreated adult rodents (3-12 months) as well as in rodents with neurodegenerative diseases such as glaucoma. With prolonged topical treatment, as many as 32% new neurons appear in all retinal layers.

Studies to examine the mechanism of this response has demonstrated that when the agonist is applied topically, it acts on specific receptors in the retinal pigment epithelium (RPE) that lie outside the neural retina. Stimulation of these RPE receptors release signaling molecules into the neural retina to induce neurogenesis from Muller glia in the retina.

In designed experiments, blast exposure will be delivered to adult rodents to test the hypothesis that eye drop application of PNU-282987 will reverse the loss of retinal neurons associated with blast exposure and recover visual function. This study will examine the loss of neurons in the retina and the loss of axons in the optic nerve before and after inducing a blast to mimic the effects of damage caused by a primary blast wave that often occurs in war zones. The blast injury will be delivered to the eyes of anesthetized adult mice (3-12 months) using a blast pressure of 26psi that is delivered to the cornea through a paint gun according to the procedure described by Hines-Beard et al. Experiments will be performed to determine if the acetylcholine agonist, PNU-282987, reverses the loss of retinal neurons typically associated with the blast exposure. Four milestones will be implemented for the first part of this study: Milestone 1: Quantification of the pressure blast on retinal neuron survival. Milestone 2: Generation of a dose-response effect of PNU-282987 on blast exposed retinas. Milestone 3: Verification of receptor specificity. Milestone 4: Quantification of morphological changes that occur in the retina and optic nerve after treatment with PNU-282987 in control and blast exposed animals.

In the second part of this study, electroretinogram (ERG) activity in the rodent eye will be recorded and analyzed to assess visual function changes before and after agonist treatment, with and without blast induced injury. Milestone 5: Assess ERG changes that occur after blast exposure before and after treated with PNU-282987.

Taken together, these experiments will be the first to determine if activation of alpha7 nAChRs in the eye can replace retinal neurons lost to blast exposure in an adult mammal and is the first study to link specific acetylcholine receptor-induced neurogenesis with change of retinal function in adult mammals. Vision loss is responsible for a reduced quality of life and a substantial burden on national healthcare systems. The results of these studies could lead to eye drop treatments that significantly improve visual function in Soldiers that experience blast exposure in combat to improve their quality of life. In addition, the results of these studies could challenge current ideas that maintain the adult mammalian central nervous system is incapable of regeneration.

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