Brief treatment with P7C3-A20 in chronic blast-mediated traumatic brain injury, one year after blast exposure, improves cognition, restores the blood-brain barrier, and reduces neurodegeneration.

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Traumatic brain injury (TBI) leads to both acute and chronic brain pathology and neuropsychiatric impairment subsequent to application of an external force to the head. Over 50 million people worldwide are affected annually by TBI, and there are currently no neuroprotective treatments that block either acute or chronic progression of TBI-induced impairment. The signature injury of military conflicts today is blast overpressure exposure, frequently from improvised explosive devices. We have previously shown that acute treatment of mice with the P7C3-class of neuroprotective compounds initiated 24 hours after blast injury blocks axonal degeneration and cognitive deficits within the first month following TBI. Because of the substantial number of patients with a more remote history of blast-induced TBI, however, we have also sought to determine whether P7C3 compounds might confer benefit when treatment is initiated chronically, one year after blast-induced TBI. We have observed that cognitive deficits persist one year after blast-induced traumatic brain injury in mice, and that initiation at this chronic time point of one month of daily treatment with P7C3-A20 reverses cognitive impairment in the Morris water maze test. P7C3 compounds are known to increase nicotinamide adenine dinucleotide levels in cells under conditions of injury or disease. Somewhat surprisingly, this reversal of cognitive deficit persisted 4 months after discontinuation of treatment with P7C3-A20. Brain tissue analyzed at this time (17 months after injury) also showed the P7C3-A20 treatment was associated with both restoration of an intact blood brain barrier as well as decreased axonal degeneration in the cortex, corpus callosum, and fimbria. Our results suggest that delayed initiation of treatment with a drug based on the P7C3-compounds might provide therapeutic benefit for patients suffering from chronic TBI, and that in addition to neurons, endothelial cells of the neurovascular unit may also benefit from the NAD-augmenting properties of P7C3 compounds.