Enhancement of Adult Hippocampal Neurogenesis by a Neurotrophic Peptide in Traumatic Brain Injury

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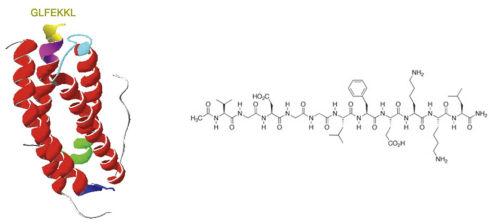
Introduction

Selective hippocampal vulnerability to trauma is the cause of long-term cognitive impairment in survivors of traumatic Brain Injury (TBI). Following TBI, there is up-regulation of neurotrophic factors in the hippocampus to preserve volume and function of the granule cell layer. Therefore, increasing adult hippocampal neurogenesis and stimulating neuronal plasticity pharmacologically could be a very useful strategy towards inhibiting cognitive decline following TBI.

Figure 1



Human CNTF and Peptide 6

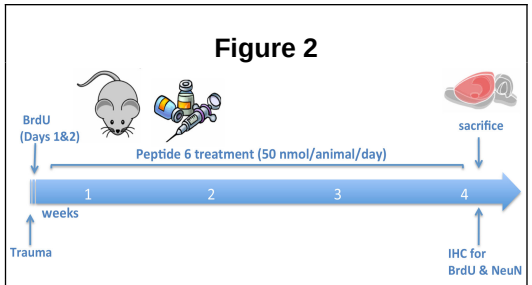
Significance

We recently discovered an 11-mer peptide (Peptide 6) corresponding to an active region of human ciliary neurotrophic factor (Figure 1) which, when given peripherally, increased numbers of proliferating and differentiating adult hippocampal neural progenitor cells (AHPs) with improvement of reference memory in mouse models of Down syndrome and Alzheimer's disease. We therefore, hypothesized a similar effect in traumatic brain injury.

Methods

Adult C57Bl6 mice were subjected to TBI using controlled cortical impact (CCI) device with 1.5 mm of cortical penetration. The animals were treated with 50nmol/animal/day of Peptide 6 or saline given as daily intraperitoneal injections for 30 days. Dentate gyrus neurogenesis was assessed by stereological analysis of cells expressing neuronal markers, doublecortin and NeuN, and BrdU uptake (Figure 2).

Figure 2

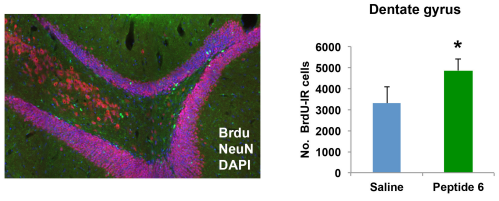


Experimental Paradigm

Results

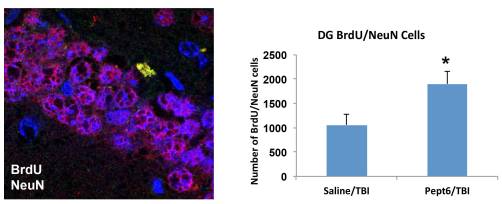
We found that, compared to saline, Peptide 6 treatment significantly increased number of proliferating progenitors in the dentate gyrus by 50% (BrdU-IR cells, mean ± SEM: 3303 ± 217 control, 4850 ± 265, p = 0.037) and enhanced neuronal commitment (BrdU-NeuN IR cells: 1057 ± 217 control; 1901 ± 265 Peptide 6, p = 0.004) by 80% (Figures 3 & 4)

Figure 3



Peptide 6 Enhances Proliferation of Dentate Gyrus Progenitors

Figure 4



Neuronal Fate Commitment in Dentate Gyrus Progenitors

Conclusions

Our results suggest that long-term treatment with Peptide 6 enhanced the pool of neural progenitor cells in the hippocampus and increased the numbers of newborn neurons in TBI mice. Further studies examining the effect of Peptide 6 on hippocampus dependent memory tasks will further elucidate its role in developing potential therapy for severe traumatic brain injury.

Learning Objectives

By the conclusion of this session, participants should be able to:

1)Describe the effect of severe traumatic brain injury on hippocampus and its effect on cognition on survivors
2)Describe the role of neurotrophic factors in enhancing adult hippocampal neurogenesis for maintenance of hippocampal cytoarchitecture.
3)Describe the potential therapeutic role of a novel small molecule based on human ciliary neurotrophic factor (CNTF) in enhancing hippocampal neurogenesis in the post traumatic brain

References

Chohan, M. O. et al. Enhancement of dentate gyrus neurogenesis, dendritic and synaptic plasticity and memory by a neurotrophic peptide. Neurobiology of aging 32, 1420-1434 (2011).
Blanchard, J. et al. Pharmacologic reversal of neurogenic and neuroplastic abnormalities and cognitive impairments without affecting Abeta and tau pathologies in 3xTg-AD mice. Acta neuropathologica 120, 605-621 (2010)
Chirumamilla, S. et al. Traumatic brain injury induced cell proliferation in the adult mammalian central nervous system. Journal of neurotrauma 19, 693-703 (2002).
Emsley, J. G. & Hagg, T. Endogenous and exogenous ciliary neurotrophic factor enhances forebrain neurogenesis in adult mice. Experimental neurology 183, 298-310 (2003)
Oyesiku, N. M. et al. Regional changes in the expression of neurotrophic factors and their receptors following acute traumatic brain injury in the adult rat brain. Brain research 833, 161-172 (1999).