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Research Report

Combination of growth factor treatment and scaffold deposition following traumatic brain injury has only a temporary effect on regeneration

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ABSTRACT

The recovery after traumatic brain injury (TBI) is hampered by the poor regenerative capacity of the brain. Today there is no treatment available that effectively restores lost brain tissue, but much research is focused on the stimulation of endogenous neural stem cells to viably and functionally repopulate the injured parenchyma. It is crucial that the therapies have a proven long-term effect on both regeneration and functional recovery to be clinically interesting. Here we have studied the induction of stem cell activation in rats at three weeks and six weeks after inducing TBI using controlled cortical impact model at a severe setting. We combined intracerebroventricular growth factor and scaffold treatment in order to accomplish an optimal effect on the stem cell regeneration. Immediately after TBI epidermal growth factor infusion with osmotic minipumps was started and continued for seven days. The pumps were removed and an extracellular matrix scaffold containing vascular endothelial growth factor was deposited into the cortical cavity. Three weeks after injury there was a positive effect of the treatment with a significant increase in neuronal and astrocytic regeneration. However, after six weeks there was no difference in the number of newly generated neurons and astrocytes in treated or untreated rats. Evaluation of tissue loss and spatial learning in the Morris water maze corroborated that the treatment had no effect at the later time point. Our results highlight the importance of long-term studies to ensure that a promising effect on tissue regeneration and functional outcome is not only temporary.

1. Introduction

Traumatic brain injury (TBI), caused by e.g., motor vehicle accidents and falls, is the leading cause of death and disabilities in young adults in the industrialized world. Many of the survivors suffer from severe disabilities for the rest of their lives, including motor deficits, impaired cognitive function and memory loss. Today there is no pharmacological treatment available to protect or restore the injured brain tissue after TBI, but there is hope in being able to use stem cell therapies to promote regeneration in the future. However, to be realized in a clinical setting, neural stem cell

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therapies need to have a proven long-term effect on neuronal regeneration and functional outcome.

It is now well established that neurogenesis in the adult brain persists throughout the entire life in the regions of the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus (Yao et al., 2012). Furthermore, it has been shown that the amount of newly generated cells can be modulated by neuropathological conditions, for example, enhanced cell proliferation has been demonstrated after experimental TBI (Blizzard et al., 2011; Chirumamilla et al., 2002; Ramaswamy et al., 2005). However, it is not clear whether this activation leads to a stable and productive neurogenesis as probably only a very limited number of surviving neurons integrate properly after injury (Kernie and Parent, 2010).

Much research has been dedicated to identifying and evaluating the effects of growth factors and other substances on endogenous stem cell proliferation and how these effects could produce functional neurons that would repair tissue and improve function. For example intracerebroventricular (i.c.v.) infusion of epidermal growth factor (EGF) has been shown to increase the number of bromodeoxyuridine (BrdU) positive cells in the SVZ and the DG one week after TBI in rats. However, four weeks after trauma the authors did not find any difference in the number of BrdU positive cells compared to untreated controls. The EGF-treatment also resulted in improved functional outcome three weeks after trauma, but no experiments were performed at later time points (Sun et al., 2010). Similar to EGF, vascular endothelial growth factor (VEGF) has been reported to stimulate adult neurogenesis and it has also been shown to act as a chemoattractant for neural stem cells in vitro (Jin et al., 2002; Zhang et al., 2003). Moreover, VEGF is known to be the key factor in the regulation of endothelial cells and vessel formation (Karamysheva, 2008). Inducing over-expression of VEGF-A using adenoviral delivery of a specific promotor was recently shown to decrease motor deficits and reduce cell death after TBI in rats (Siddiq et al., 2012). These previous investigations clearly indicate that both EGF and VEGF are

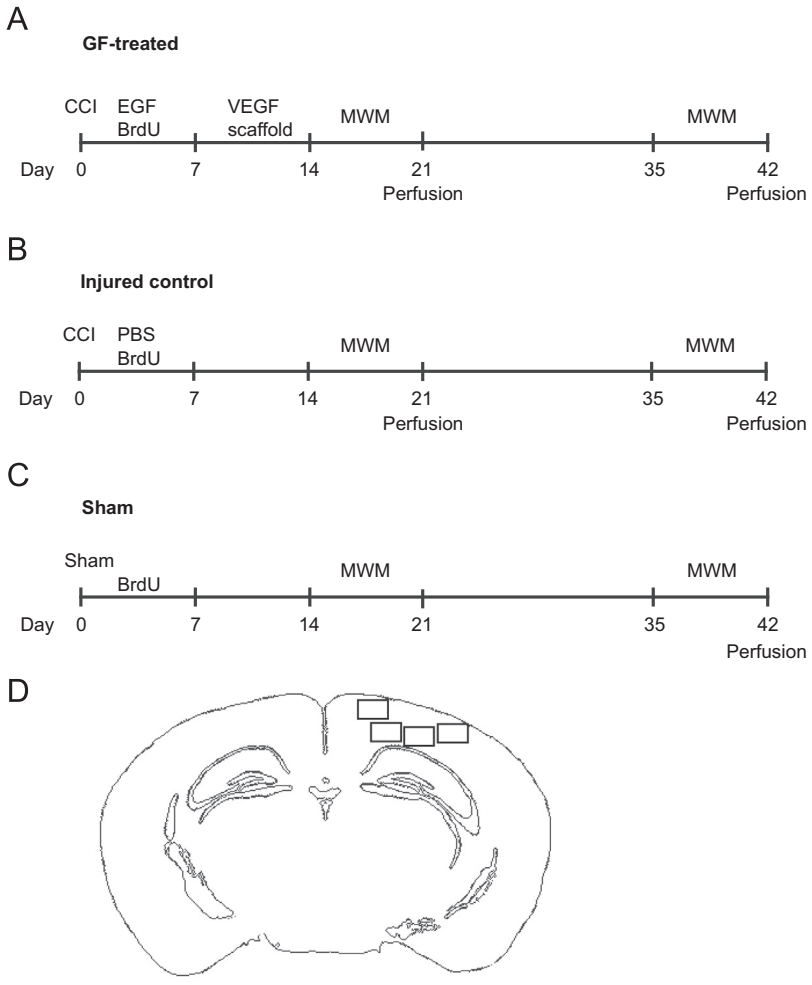

Fig. 1 – The rats were sacrificed for tissue analysis at either day 21 or day 42 post-injury (Perfusion). In order to label dividing stem and precursor cells the rats received daily BrdU injections during the first week following CCI (BrdU). To test the spatial learning Morris water maze (MWM) experiments were performed days 36–39 post-injury (A). In GF-treated rats an osmotic mini pump with EGF was connected to the contralateral lateral ventricle directly after the CCI. At day 7 the EGF-pump was removed and the cortical cavity was filled with an ECM-scaffold supplemented with VEGF. (B) TBI control rats had their mini-pumps filled with saline and received no scaffold at day 7. (C) Sham operated controls received the surgery, but neither pump nor scaffold. (D) Selected fields around the injury site were photographed and analyzed.