

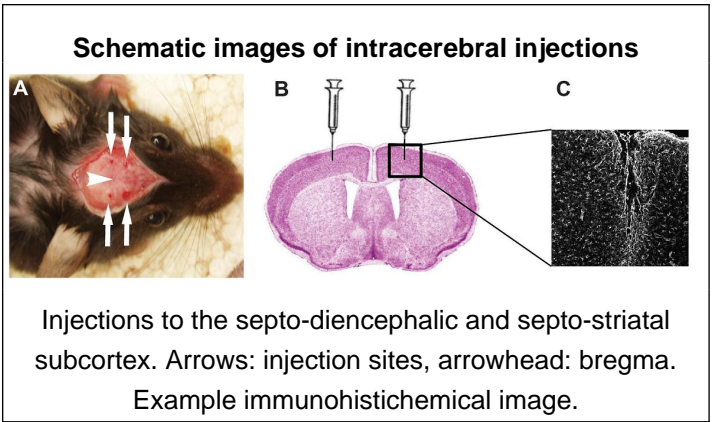
Comparison of Vascular Growth Factors in the Murine Brain Reveals Placenta Growth Factor as Prime Candidate for CNS Revascularization



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Introduction

Angiogenesis is the vascular growth factor promoted formation of new blood vessels from the preexisting vasculature. Therapeutic angiogenesis via gene vector delivery has been successfully used to increase blood perfusion in multiple tissues. Bypass procedures in the central nervous system (CNS) remain technically challenging, hindered by complications and often fail to prevent adverse outcome, such as stroke. Thus there is an unmet clinical need for a safe and effective revascularization of the CNS. Vascular endothelial growth factors (VEGFs) are promising candidates for revascularization, however, their effects appear to be tissue specific and their potential in the CNS has not been fully explored.

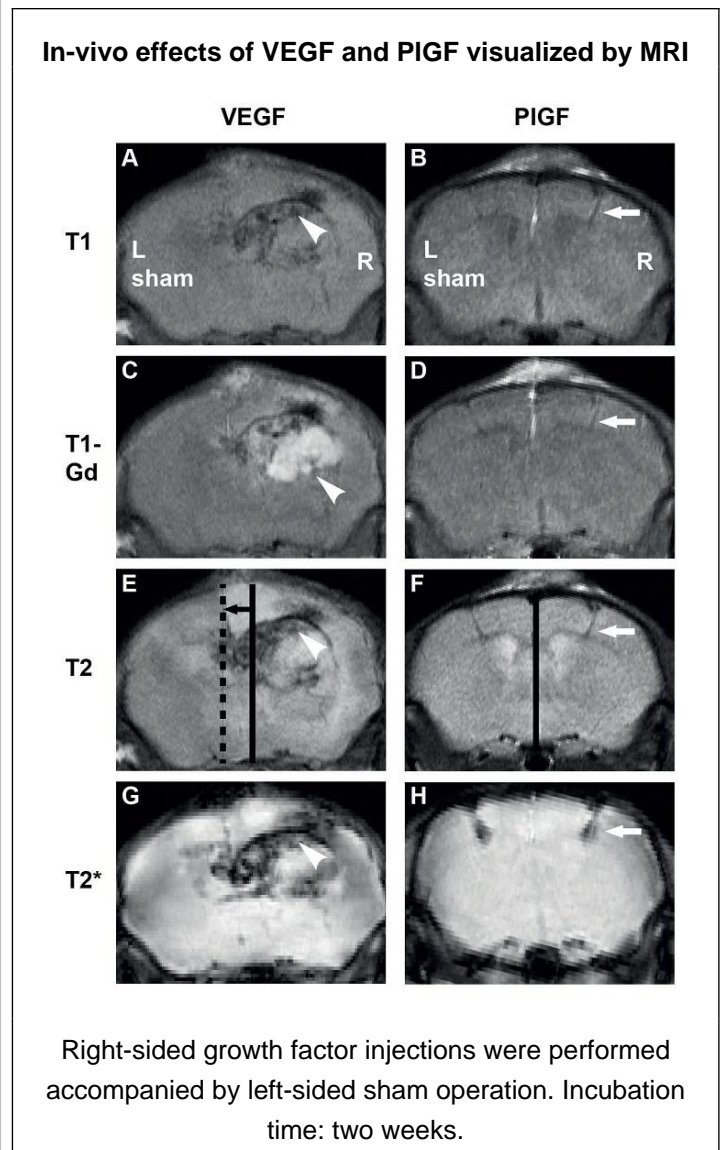


Methods

To test growth factors for angiogenesis in the CNS, we characterized the effects of endothelium-specific growth factors on the brain vasculature and parenchyma. Recombinant adeno-associated viral vectors (AAV) encoding the human and murine vascular growth factors were injected transcranially to the frontoparietal cerebrum of mice. Angiogenesis, mural cell investment, leukocyte recruitment, vascular permeability, reactive gliosis and neuronal patterning were evaluated by 3-dimensional immunofluorescence, electron microscopy, optical projection tomography and magnetic resonance imaging, two weeks after gene transfer.

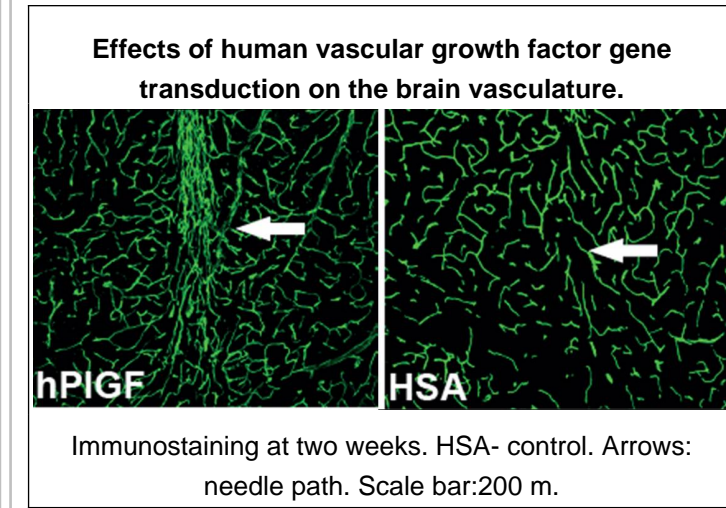
Results

Placenta growth factor (PIGF) stimulated robust angiogenesis and arteriogenesis without significant side effects, whereas VEGF and VEGF-C incited growth of aberrant vessels, severe edema and inflammation. VEGF-B, angiopoietin-1 and angiopoietin-2 had minimal effects on the brain vessels.



Conclusions

PIGF emerged as the most efficient and safe angiogenic factor, hence making it a prime candidate for therapeutic CNS revascularization.



Learning Objectives

Our results identified PIGF as a strong candidate for therapeutic revascularization of the CNS. These findings should lead to the development of new clinical approaches, including the combination of growth factor therapy with vascular bypass surgeries.

