THE ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN POST-STROKE RECOVERY

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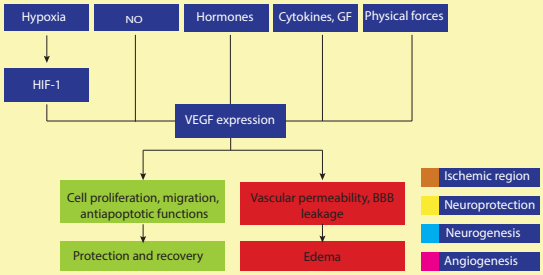
Objectives

- Explain what a stroke is and how injuries are produced.
- Briefly describe post-stroke regeneration processes.
- Analyze the role of endogenous VEGF in such processes.
- Check out different research work about its possible application in therapeutics.

Introduction

- A stroke is a cerebrovascular disease resulting from reduction or interruption in cerebral blood flow. Insufficient delivery of oxygen and glucose to support cellular homeostasis causes depletion of ATP stores. This induces multiple processes, also known as the ischemic cascade, that lead to cell dead .

The role of endogenous VEGF in post stroke recovery



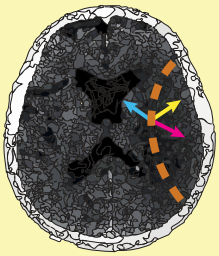


Figure 1.VEGF effects in acute ischemic stroke.
A horizontal section of the human brain shows an acute infarct within the territory of the middle cerebral artery (dotted line). VEGF-A is induced in the ischemic border zone and acts on local neurons and endothelial cells to promote neuroprotection (yellow arrow) and angiogenesis (pink arrow). VEGF-A also stimulates neurogenesis (blue arrow) in the subventricular zone, from which new neurons migrate to the site of ischemia. ***(Greenberg & Jin, 2013)***

VEGF-based therapies

Exogenus VEGF administration

Efects of VEGF administration

- VEGF administration, was associated with an infarct size reduction ranging from 34% to 47% and improved clinical outcome.

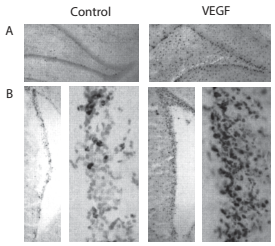


Figure 2.VEGF stimulates BrdUrd incorporation into neuroproliferative zones of rat brain in vivo.
BrdUrd was localized by immunohistochemistry in hippocampus (A) and rostral SVZ (B). Note that BrdUrd incorporation is not confined to neuroproliferative zones, but extends, for example, into the dentate hilus in (A) consistent with the labeling of both neuronal and non-neuronal cells. ***(Jin et al., 2002)***

Route of administration

- There is great variability between different protocols in terms of the administration route.

Time of administration

- Post- ischemic (1hr) administration of rhVEGF165 significantly increases BBB leakage, haemorrhagic transformation and ischemic lesions, whereas VEGF administration after the actue phase (48 hrs) was associated with angiogenesis enhancement and functional improvement.

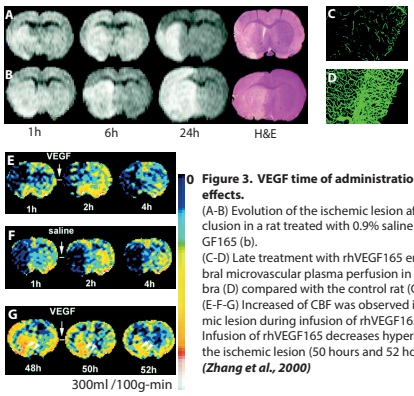


Figure 3. VEGF time of administration and its effects.
(A-B) Evolution of the ischemic lesion after MCA occlusion in a rat treated with 0.9% saline (a) or rhVEGF165 (b).
(C-D) Late treatment with rhVEGF165 enhances cerebral microvascular plasma perfusion in the penumbra (D) compared with the control rat (C) .
(E-F-G) Increased of CBF was observed in the ischemic lesion during infusion of rhVEGF165 (2 hours) (E). Infusion of rhVEGF165 decreases hyperemic areas in the ischemic lesion (50 hours and 52 hours) (G). ***(Zhang et al., 2000)***

Dose

- VEGF enhances vascular proliferation in dose dependent manner, but neuroprotection of ischemic brain by exogenous VEGF does not necessarily occur with angiogenesis, as different dosages of VEGF165 can injure rather than promote recovery of nervous tissues.

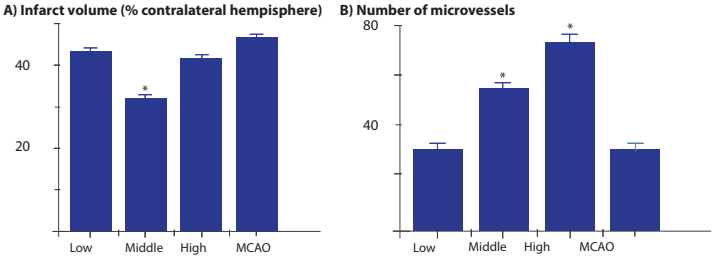


Figure 4. Dose-dependent effects of VEGF
(A) Quantitative effects of VEGF on infarct volume after MCAO (mean±SE) compared to saline, middle dose of VEGF significantly reduced infarct volume after MCAO. P < 0.01. (B) Middle and high doses of VEGF significantly increased the number of microvessels in the boundary regions of ischemia compared to stroke rats with saline treatment. ***(Yang et al., 2009)***

Pre- morbid status

- Pre- existing chronic diseases such as diabetes or hypertension can complicate therapeutic angiogenesis, since these diseases directly affect nervous tissue's blood vessels.

Combined therapy: stem cells + VEGF

Mesenchymal stem cells (MSCs)

- This therapeutic approach may be used beyond hyper actue phase of stroke.
- Survival and regenerative capabilities of transplanted MSCs can be enhanced by hypoxic preconditioning of the MSCs.
- Transplantation of MSCs containing a modified VEGF gene may provide a better autologous cell transplantation therapy for stroke than transplantation of naïve MCSs.

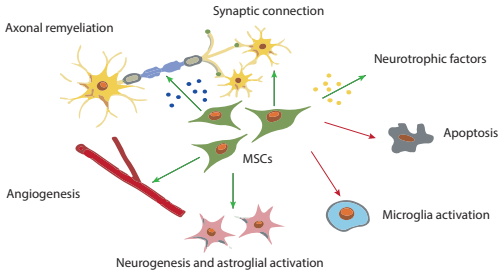


Figure 5. Potential therapeutic mechanisms of neurorestoration using mesenchymal stem cells.
MSCs secrete a variety of neurotrophic factors that promote endogenous neuronal growth, induce angiogenesis, neurogenesis and astroglial activation, encourage synaptic connection and axonal remyelination, decrease apoptosis, and regulate microglial activation primarily through paracrine actions. ***(Seo & Cho, 2012)***

Neural progenitor cells (NPCs)

- The graft itself is a useful vehicle for GF delivery, promoting the survival of NPCs. Moreover, transplantation of VEGF-expressing NPCs supports angiogenesis in the brain, wich may contribute to brain repair.
- NPC transplantation combined with VEGF administration is associated, with reduced cerebral atrophy, increased vascular density and better functional recovery.

Conclusions

- After the onset of a stroke, hypoxic conditions induce VEGF synthesis, which protects the brains and enhances neurogenesis and angiogenesis...
- But thus endogenous VEGF production is usually insufficient to entirely protect the brain.
- There is multiple evident about the benefitial effects of VEGF administration (alone or combined with stem cells) in post-stroke recovery.
- However, we can not underestimate its potential negative effects, as BBB leakage and edema formation.
- In order to develop specific and efficient therapies, a better understading of VEGF's mechanisms of action is required.

Selected references

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