VEGF enhance the permeability of the blood-brain barrier
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Objective: The blood-brain barrier (BBB) is a tightly regulated barrier that strictly controls the exchanges between the blood and brain components. The vascular endothelial growth factor (VEGF) is one of the most important growth factors in the process of angiogenesis and vasculogenesis. We aim to (1) increase the permeability of BBB by the injection of VEGF so as to make the central nervous system (CNS) drug delivery convenient; (2) find an effective method for the measurement of the extent of the BBB permeability by MRI in vivo.

Methods and materials: In this study, we used 18 KM mice, which were divided into two groups: 12 in histopathology group and 6 in MRI group, respectively. The 12 mice (18-22g) were randomized into 3 subgroups. Group 1 received 200ul saline only, group 2 & group 3 received recombinant human VEGF-165 (0.015mg/ml, dissolved in saline) 200ul through the tail vein and was treated for 4h and 12h respectively. The mice received 0.075ml Evans Blue (2%; 3ml/kg) after treated as above and allowed Evans Blue to circulate for 30 minutes. The 12 mice in histopathology group were sacrificed 0.5h after the injection of Evans Blue and perfused with saline and paraformaldehyde (PFA) sequentially. Subsequently, the brains were removed and placed in PFA on ice. After 12 hours infusion in PFA, brains were washed with PBS (0.01M) three times every 10 minutes. Then the brains were coated with agarose (4%), and vibratio microtome (Leica, Germany) was used to get the brain slides. The slides were immediately put under the fluorescence microscope thereafter to detect red fluorescence.

Results: (1) Histological results showed Group 3 had a significant higher permeability of blood vessel than Group 1 (Figure 1). Group 2 had a slightly higher permeability of blood vessel than Group 1 (Figure 1), the difference was not obvious. (2) MRI examination showed Group B had a higher signal intensity of brain parenchyma (P<0.001) than Group A (Figure 2). The extravasation of Gd-DTPA observed within the brain showed an impairment of the BBB integrity. Minimal edema between these two groups in MRI group was also investigated, however, no significant difference was found from picture obtained.

Conclusions: (1) The exogenous VEGF can enhance the BBB permeability and may induce neovascularization. The permeability of the BBB can be modulated by venous injection of VEGF and may be a new direction to deliver drugs to the CNS. (2) MRI has a good sensitivity in the detection of BBB leakage compared with histological method and may be an ideal method for the measurement of the permeability of the BBB in vivo.

Reference: