The Laser Technologies of Targeted Opening of Blood-Brain Barrier for Drug Brain Delivery

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***Abstract* - Here we show the photodynamic treatment (PDT) causes significant increase in the permeability of the blood-brain barrier (BBB) in healthy mice. Using different doses of laser (635 nm, 10-40 J/cm^2) and photosensitizer (5-aminole-vulinic acid – 5-ALA, 20 and 80 mg/kg, i.v.), we found the optimal PDT for the reversible opening of BBB that is 15 J/cm^2 and 5-ALA, 20 mg/kg, when the brain tissues recover 3 days later. Further increase in the laser or 5-ALA doses has not amplifying effect on the BBB but associated with severe damages of brain tissues. These results can be good informative platform for the further studies of new strategies in brain drug delivery and for the better understanding of mechanisms underlying cerebrovascular effects of PD-related fluorescence guided resection of brain tumor.**

I. Introduction

The blood-brain barrier (BBB) is a gatekeeper, which locates on the endothelial cells of microvasculature and controls the passage of blood-borne agents into the brain tissues playing an important role for the health of the central nervous system. These protective mechanisms restrict the entrance of many drugs into the brain. There are 7000 drugs, which are registered in the Comprehensive Medicinal Chemistry database but only 5% of them are available to treat the neuronal diseases due to reason that antibodies, recombinant proteins, therapeutic gene and most small molecules simply can not penetrate BBB. This is the reason why the approaches to open BBB have received significant attention from researches around the world in the last four decades. There are more than 70 different physical, chemical and biological methods for overcoming of the BBB. However, no methods are developed yet, which are widely used in daily clinical practice for the opening of BBB due to their invasiveness and challenges in performing.

II. Material and Methods

Experiments were carried out in mongrel mice weight 20 g (n=103). The animals were divided into five groups: 1) intact, without laser irradiation (the control group); 2-4 included mice after laser irradiation with different laser doses: 2) 10 J/cm^2; 3) 15 J/cm^2; 4) 20 J/cm^2; 5) 40 J/cm^2.

The photodynamic effects (PDT) on the BBB performed 30 min after intravenous injection of 5-ALA (20 mg/kg i.v.) and using laser 635 nm (10, 15, 20 and 40 J/cm^2).

To evaluate the BBB permeability we used: 1) the spectrofluorometric assay of Evans Blue dye (EBd, (2 mg/25 g mouse, iv) extravasation; 2) confocal microscopy of FITC-dextran 70 kDa (4 mg/25 g mouse, iv) extravasation; 3) histological analysis of BBB permeability to solutes.

III. Results

Our results on healthy mice clearly show the small dose of PDT (635 nm, 15 J/cm^2) with concentration of 5-ALA, 20 mg/kg (i.v.) is optimal for the reversible BBB opening for high weight molecular substances such as EBd (68 kDa) and dextran (70 kDa). The further increase in light doses has not amplifying effect on the BBB. However, increasing of 5-ALA concentration is accompanied by severe disruption of the BBB resulting in injuries of brain tissues (perivascular edema). We believe that these results are of high importance for the deeper understanding of PDT effects on the cerebral vasculature and its further applications in drug brain delivery.

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