Transient Optical Opening of the Blood-Brain Barrier by Laser Excitation of Plasmonic Nanoparticles

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Technology description

The blood-brain barrier (BBB) poses a low permeability to most drugs and poses a significant challenge to effective treatment of brain diseases. The BBB restricts the delivery of most drug molecules into the brain by tight junctions (TJs) that seal gaps between adjacent endothelial cells, displaying low permeability and high electrical resistance. Herein, we present a novel solution that implements TJ-targeting plasmonic gold nanoparticles to open the BBB upon excitation by ultrashort pulsed laser both in vitro and in vivo. A significant advantage of this novel BBB opening approach is the high optical resolution achieved to investigate drug accumulation. This method can be used to investigate infiltrating gliomas in brain regions that do not show contrast enhancement in MRI, which – beyond invasive and dangerous biopsies - have been inaccessible for drug penetration assessments. Results indicate that pulsed laser excitation of plasmonic nanoparticles effectively disrupts the TJs and transiently open the BBB, serving as an informative platform for drug delivery to the brain.

Technical Summary:
Plasmonic nanoparticles – of varying sizes and geometries - and gold nanoparticle coated liposomes (AuLip) can be selected for their absorption peak in the near-IR spectrum (700-1000nm), which can be excited by short laser pulses. It is reported that ultrashort laser pulse excitation (nanoseconds or less) leads to nanoscale thermal and mechanical effects (including plasmonic nanobubbles). This results in extremely selective effect on the targeted TJs and temporarily opens the BBB, without significant global heating. Furthermore, AuLip is capable of carrying drugs in the liposome and plasmonic nanoparticles can also be conjugated with a polymer layer on the outside that can absorb anticancer drugs for targeted delivery to the brain.

The method was validated in both in-vitro (hCMEC/D3 cell monolayer) and in-vivo mouse models. Transendothelial electrical resistance (TEER) and permeability measurements were used to characterize nanoparticle effects on opening the BBB in-vitro. Immunocytochemistry (ICC) staining results shows colocalization of the nanoparticles with the TJ protein target, JAM-A. Laser excitation of the nanoparticle-treated model led to the TEER value dropping by 50% & permeability of 40 kDa dextran increased 23-fold; the TEER value for the untreated model was unchanged with laser illumination.

Reversible disruption of the BBB is shown, as the TEER value recovers to 100% within 6 hours after applying the laser pulse.
For the in-vivo testing, BBB opening was demonstrated by visualizing extravasation of Evans Blue (EB) in the CNS, which indicates permeability of the BBB. TJ targeting nanoparticles, when compared with no targeting (polyethylene glycol, or PEG), decreased spleen accumulation by 4-fold and increased accumulation in the brain by 4-fold – demonstrating the TJ targeting to effectively change overall biodistribution of the nanoparticles. The effect of laser pulse energy was shown to scale directly with increased EB extravasation, with a pulse energy threshold for BBB opening identified at 5 mJ/cm^2. BBB recovery after opening was shown to occur as soon as one hour after laser treatment, as mice injected with EB at this time point showed less EB extravasation than mice injected with EB before laser illumination. Histopathology staining revealed that laser pulses, even at higher energy (25 mJ/cm^2), do not cause significant damage to cerebral blood vessels, astrocytes, and neurons. These results demonstrate that the area of BBB opening may be controlled optically and with high spatial resolution.
Value Proposition:
We present a novel method of optically-opening the BBB with high spatial resolution that has been demonstrated to facilitate the transport of macromolecules into the brain while being minimally-damaging, especially compared with the current state of the art. This model may further be used for drug penetration assessments and as drug delivery platform for new and existing anticancer agents.
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Application area

Drug Penetration Assessments (e.g. for investigation of infiltrating gliomas)
BBB Penetration Platform for Existing Anticancer Drugs
Drug Delivery to the Brain

Advantages

High Resolution- Area of BBB opening may be controlled optically, by varying the laser power, laser size, and number of pulses
Reversible– Transient opening of BBB is demonstrated, with partial BBB recovery occurring as soon as 1 hour after laser activation for in vivo model
Localized- Heating AuNPs with a laser pulse creates PNBs that generate a mechanical impact without significant global heating beyond the nanobubble
Drug Delivery- Allows the use of chemotherapy drugs that are ineffective due to constraints from the BBB; in-vivo biodistribution studies of TJ-targeting AuNPs revealed 4-fold increase in brain accumulation
Minimally Damaging- Laser pulses do not lead to significant damage to blood vessels, astrocytes, or neurons

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