SF05-S2 Recent Studies of Therapeutic Ultrasound
16:15-16:40 Room 203
Chairperson(s): Jae Young Lee *(Seoul National University Hospital, Korea)*
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FUS-Mediated Unbinding of Phenytoin from Plasma Proteins for Chronic Focal Epilepsy Suppression

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Background: Pharmacological intervention is considered the frontline treatment for epilepsy, but the efficacy of anti-epileptic agents, such as phenytoin (PHT), is reduced by plasma protein binding (PPB) that sequesters therapeutically effective drug molecules within the blood. An increase in systemic dose elevates concentration of unbound drug but would accompany increased risk of drug side effects. Thus, an alternative technique to regionally increase the concentration of unbound PHT has been sought after.

Methods: We present a non-invasive, low-intensity pulsed transcranial focused ultrasound (FUS) technique, operating at 600 kHz and spatial-peak pulse-average intensity (ISPPA) of 5 W/cm2, to enhance the efficacy of PHT by transiently disrupting its binding to serum albumin in a region-specific manner, thus promoting PHT delivery across the blood–brain barrier (BBB). First, effects of different combinations of pulse duration and duty cycles of sonication on unbinding efficiency were evaluated using equilibrium dialysis, and we identified the acoustic parameter that yielded the highest PHT unbinding from albumin. Then, in the subsequent animal experiments, Sprague-Dawley rats having chronic mesial temporal lobe epilepsy (mTLE; via intrahippocampal kainic acid injection) received four sessions of intraperitoneal PHT injection (for 2-week period), each followed by 30 min of FUS delivered to the ictal region (PHT+/FUS+, n = 10). Two additional groups of mTLE rats (n = 10 each) underwent the same experimental procedure, without receiving FUS (PHTONLY) or without receiving PHT (FUSONLY). The seizure-suppressive effects of these (three) experimental conditions were evaluated by measuring seizure indices (count, duration, and amplitude of ictal events associated with behavioral seizures based on a modified Racine scale) obtained from 24 h of electroencephalogram (EEG)/video recording for 2 weeks, before and after interventions. The safety of the FUS was evaluated by post-FUS behavioral observation and histological examination of brain tissue obtained ~2 days after and a month after the last sonication session. The integrity of the BBB was also examined by intravenous trypan blue injection immediately after the sonication.

Results: Equilibrium dialysis demonstrated that sonication having higher acoustic energy deposition per time (50% duty cycle) offered a superior unbinding property, showing ~16% increase of unbound drug concentration compared to the unsonicated control condition. From the animal experiment, FUSONLY condition did not show any suppressive effect in any of the seizure indices while the animals under PHT+/FUS+ showed ~57% reduction of the number of ictal events, more than a 2-fold decrease compared to PHTONLY condition that yielded ~27% reduction. The mean duration of the ictal events was also significantly decreased (by ~35%) during PHT+/FUS+ conditioncompared to those from PHTONLY and FUSONLY conditions. The histological analysis and trypan blue injections did not show any signs of brain damage or BBB disruption caused by the FUS.

Conclusions: These results demonstrated that the non-invasive, low-intensity FUS technique enhanced anti-epileptic efficacy of PHT in a rodent model of chronic focal epilepsy by region-specific unbinding of the pharmacological agent from plasma

proteins.

Keywords: focused ultrasound, drug delivery, plasma protein binding, focal epilepsy, phenytoin