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Acoustic Cluster Therapy for Enhancing Blood-Brain Barrier Permeability

Andreas Aslund *

Department of Physics, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

***Corresponding author:** Andreas Aslund, Department of Physics, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; E-mail: andreasaslund@gmail.com

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Introduction

The Blood-Brain Barrier (BBB) is a key barrier to medicine delivery for brain illnesses, and there is currently no standardized way to get through it. Focused ultrasound in combination with gas-filled micro bubbles is one way for disrupting the BBB locally and transiently. The micro bubbles utilized, on the other hand, were designed for ultrasound imaging rather than BBB disruption. The potential innovative Acoustic Cluster Therapy (ACT), which has recently been used in combination successfully treat subcutaneous tumors of human prostate cancer in mice, is described here. Electrostatic interactions lead to the conjugation of micro bubbles to liquid oil micro droplets in ACT. The micro droplet phase transforms into a bigger bubble that transiently lodges in the microvasculature when activated in an ultrasonic field. Further insolation causes the triggered bubble's volume to oscillate, resulting in biomechanical consequences that improve BBB permeability. With an acoustic power 5-10 times lower than that used for traditional micro bubbles, ACT was able to securely and temporarily permeabilize the BBB and successfully transfer small and big compounds into the brain.

The Blood-Brain Barrier (BBB) keeps the brain in a state of equilibrium and protects it from hazardous substances. Unfortunately, unless active transport of the substances is possible, the BBB prevents >98 percent of tiny medicines (600 Da) and all larger therapeutic molecules from entering the brain. As a result, the presence of an intact BBB restricts the distribution of a wide range of therapeutic agents, including anti-cancer and anti-viral medications, as well as innovative treatment approaches that are not yet ready for clinical application. As a result, disorders such as brain cancer, Alzheimer's disease, and Amyotrophic Lateral Sclerosis (ALS) remain incurable. Every drug lead must be investigated for new ways to breach the BBB, putting a significant limit on the development of medicinal therapy for brain illnesses. Focused Ultrasound (FUS) in combination with micro bubbles has been studied in various pre-clinical settings to promote BBB permeability since its inception in 2001. In short, insolation of the micro bubble-containing vascular compartment causes a range of biomechanical consequences that increase endothelial barrier permeability both paracellularly and transcellularly. Extravasation, distribution, and absorption of drug molecules in the target tissue are all improved as permeability increases. Two distinct clinical trials are now evaluating this method. Acoustic Cluster Therapy (ACT), a recently proposed approach for ultrasound-mediated, targeted medication delivery, uses similar mechanics to conventional micro bubbles, but overcomes some of the latter's drawbacks. The ACT formulation concept has been explored in detail previously.

In a nutshell, the ACT formulation is made up of negatively charged micro bubbles and positively charged oil micro droplets that form an electrostatic combination. Micro bubble/micro droplet clusters developed to be stable *in vivo* make up the active moiety. Ultrasound is administered to the diseased area after intravenous injection of the clusters, and the micro bubbles transfer sonic energy to the associated droplets, which undergo a liquid-to-gas phase change (the "activation" step). The generated ACT-bubbles expand quickly to about 25 m and are briefly deposited in the local capillary network, momentarily stopping blood flow for up to 10 minutes. Further ultrasound application (the "enhancement" step) causes volume oscillations in the ACT-bubbles, resulting in non-thermal mechanisms like cavitation and shear forces that increase the local permeability of the vasculature, increasing drug transport across the capillary wall and through the extracellular matrix. Because ACT bubbles are three orders of magnitude higher in volume than conventional contrast micro bubbles, they will have a much greater biomechanical effect. Furthermore, throughout a substantial section, the ACT bubble is in intimate contact with the endothelium wall, providing optimum septum.

Healthy female sprague dawley rats (NTac:SD; Taconic), 8-12 weeks old with a weight of 240-280 grams, were used. All experimental procedures were conducted in compliance with protocols approved by the Norwegian animal research authorities. Animals were housed in a specific pathogen free environment at a 12h night/day cycle with controlled temperature and humidity. Food and water were provided ad libitum.

Ultrasound Setup and Treatment Regimen

A 1 MHz FUS transducer (Imasonic SAS) with a diameter of 50 mm and a focal length of 125 mm (f-number 2.5) was used. The transducer was positioned in a water bath and a specially designed Magnetic Resonance Imaging (MRI) bed, with the animal in a supine position, placed on top of the water tank. The skull of the animal was positioned approximately 120 mm from the transducer. The animal was sedated by gas anesthesia (isoflurane ~4% and 2% induction and maintenance, respectively, in 78% medical air/20% O2). The head of the animal was shaved using a trimmer, and depilatory cream was applied to the shaved area for 1 min to remove remaining hair. The tail vein was cannulated (BD Neoflon 24G, Becton Dickinson & Co), and the animal placed on the MRI bed. Omniscan (1 ml/kg, 0.5 mmol gadododiamide/kg) was injected and MR images were recorded. Sonazoid™ (1 ml/kg) or ACT (1 ml/kg) was injected and the cannula was flushed with 0.1 ml of 1 U/ml heparin. Immediately after injection, the ultrasound treatment was initiated. The treatment was divided into an activation step followed by an enhancement step using the same transducer and the same sonication sequence with two different Mechanical Indexes (MIs). The MI was calculated from the estimated in situ pressure, assuming 40% attenuation of the ultrasound power through the skull of the animal.

Analysis of BBBD

To evaluate the effect of BBBD, the intensity of the contrast agent in the MR images from each treatment region was estimated. When BBBD was visibly detectable, an ROI was drawn around the opened

area and the same ROI was used on the non-treated contralateral side of the brain. The ratio of the average intensities of the ROIs was calculated using Image. Positioning of the ultrasound was manual, thus the exact coordinates for the BBBD was not available. To quantify the BBBD, it was therefore required to be able to observe the contrast agent in the image. Hence, quantitative data is only available for 3 of the 5 groups.

The present study demonstrates that ACT can be utilized to open the BBB in a safe manner, using a lower pressure FUS regimen than regular contrast micro bubbles. ACT is clearly more efficient than regular micro bubbles in opening the BBB in combination with ultrasound. The ACT treatment induces a significantly enhanced extravasation of gadodiamide as well as delivery of macromolecules. This study demonstrates a new application for ACT which previously has shown great promise in enhancing the delivery of co-injected drugs to solid tumors growing in mice and in treating tumors growing in mice.