Using image-guided focused ultrasound to enhance delivery of antisense oligonucleotides across the BBB to the murine brain.

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease with extremely limited therapeutic options. Abnormal accumulation of misfolded and aggregated proteins in the soma of motor neurons is one of the main pathological hallmarks of ALS. Hence, reducing the burden of misfolded protein in motor neurons has emerged as a promising therapeutic approach to control the disease. Antisense oligonucleotides (ASOs) carry the potential to effectively silence proteins with gain-of-function mutations, such as superoxide dismutase 1 (SOD1). However, the extremely poor blood-brain barrier (BBB) penetration of ASOs and invasiveness of current intrathecal delivery methods, warrant the development of alternative strategies for the delivery of ASOs to the central nervous system (CNS). In the current study, we report the effective delivery of a next-generation SOD1 ASO (Tofersen) into the brain of mice using calcium phosphate lipid nanoparticles (CaP lipid NPs) following systemic delivery. Different ultrasound exposure levels, microbubble (MB) doses, and exposure times were tested to determine the optimal conditions for BBB opening. For the first time, we demonstrate the superior capability of transcranial focused ultrasound (FUS) with intravenously administered microbubbles to significantly improve the delivery of ASO-loaded nanoparticles into the mouse brain compared to control mice receiving FUS without microbubbles. The NP uptake in the brain was >3.5-fold higher in the case of FUS group with MBs compared to the control group without MBs. Further in vivo evaluation of this strategy could lead to the development of a promising new approach for therapeutic delivery to treat ALS in patients.