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Trans-blood-brain barrier delivery of compounds at pharmacologically relevant molecular weights in the hippocampus of mice using Focused Ultrasound

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Molecular engineering has recently contributed immensely to the development of neuropharmaceuticals. However, most of these compounds are greater than 400 Da, which are too large to traverse the brain's natural defense, the blood-brain barrier (BBB). In this study, molecular delivery at pharmacologically relevant molecular weights through a Focused Ultrasound (FUS) induced BBB opening was investigated. The left hippocampus of mice (n=13) was sonicated (frequency: 1.525MHz, pressure: 0.64MPa, duty cycle: 20%, duration: 1-min) in vivo through the intact skin and skull following intravenous injection of microbubbles (SonoVue®; 25μl). After sonication, otherwise BBB-impermeable fluorescent-tagged dextrans at various molecular weights were administered intravenously. Ex vivo fluorescent microscopy determined BBB opening by a significant increase in fluorescence in the left over the right hippocampus. The threshold for the molecular weights allowed through the hippocampal BBB was between 70k and 2,000k Da. Smaller compounds (i.e., 3k Da) were more spatially uniformly deposited throughout the hippocampus than larger (i.e., 70k Da) compounds. In conclusion, dextrans at neuropharmaceutically-relevant sizes were deposited in the left hippocampus of mice. This study thus demonstrates that FUS-induced BBB opening could allow neuropharmaceuticals previously impermeable to the BBB, such as inhibitors and antibodies, to target tissue they were designed to treat.