Ultrasound-responsive nanodroplets for localised anaesthesia

Harriet Lea-Banks[1,2], Meaghan O'Reilly[1,2], Kullervo Hynynen[1,2,3]
[1]Physical Sciences Platform, Sunnybrook Research Institute, Toronto, Canada, [2]Department of Medical Biophysics, University of Toronto, Toronto, Canada, [3]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Canada

Background, Motivation and Objective

Nanodroplets are liquid-filled nano-scale particles that have been used as ultrasound imaging agents for over 3 decades, and have recently gained popularity as potential drug carriers. When exposed to ultrasound, nanodroplets undergo vaporisation, transforming into microbubbles and releasing their therapeutic cargo. In this study we have shown that commercial microbubbles can be loaded with an anaesthetic and condensed into nanodroplets for localised anaesthesia in the brain. Building on work by Airan *et al.* (2017), we have shown localised anaesthesia of the motor cortex in rats as a proof of principle for study and treatment of the brain.

Statement of Contribution/Methods

Developing work by Sheeran *et al.* (2017) in converting commercial microbubbles into nanodroplets, Definity microbubbles were filled with decafluorobutane and loaded with pentobarbital, condensed into 200 nm droplets and purified. Localised drug delivery *in vitro* and *in vivo* was achieved using a 0.58 MHz focused transducer, triggering droplet vaporisation and drug release. Pressures required for vaporisation were assessed using a control algorithm based on the detection of ultraharmonic emissions. MRI-guided focused ultrasound was used to target one side of the motor cortex in rats, triggering release of the anaesthetic. Motor deficit following localised anaesthesia was assessed with behavioural tests.

Results/Discussion

Acoustic emissions produced by vaporising nanodroplets were found to be indicative of drug release. Nanodroplets had a circulation half-life *in vivo* of 7.8 +/- 1.3 min, significantly greater than commercial microbubbles. Following treatment with drug-loaded nanodroplets and focused ultrasound, 7 of 8 rats showed contralateral hind limb weakness and fore limb asymmetry in behavioural tests, indicating localised anaesthesia of the motor cortex. 20.5 ± 14 % deficit in contralateral motor ability was found in treated animals, a significant decrease compared to controls ($p<0.01$). Full recovery in behaviour was seen 24 hours post-treatment, and MRI showed no signs of blood brain barrier disruption or damage. We have shown that ultrasound-responsive nanodroplets formed from commercial microbubbles are a viable method of delivering anaesthetics to specific locations in the brain.

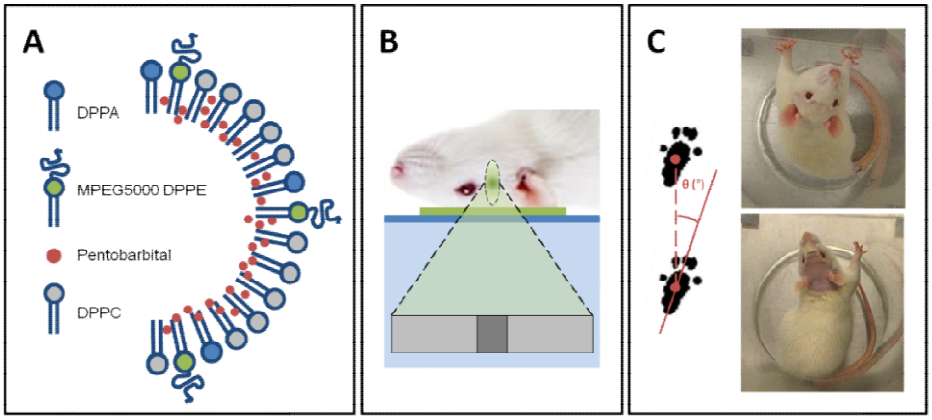

Figure 1. Schematics of pentobarbital-loaded lipid nanodroplet composition (A), focused ultrasound system targeting the motor cortex (B), and example behavioural assessment images of gait analysis and paw preference (C)