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Numerical modelling of nanoparticle-mediated drug delivery across blood-brain barrier using focused ultrasound

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Introduction

The treatment effectiveness against brain cancer remains disappointing. This can largely be attributed to the blood-brain barrier (BBB) that successfully blocks over 98% of drugs in blood under intravenous administration. Focused ultrasound has been found as a promising means to temporarily disrupt the BBB, enabling the anticancer drugs to enter the tumour tissue for cell killing. However, the performance of the combination treatment using focused ultrasound and nanoparticles are yet to be understood.

Methods

In this study, a mathematical model is established to examine the effects of focused ultrasound-induced BBB disruption on the delivery of nanoparticle-encapsulated doxorubicin. The model consists of several governing equations to describe the temporal BBB disruption and recovery, transport of nanoparticles and released drugs in tissue by convection and diffusion, cell uptake, drug elimination by physical degradation and bioreactions, etc. The modelling study is based on a 3-D realistic brain tumour model extracted from patient medical images. Drug exposure over time is adopted to evaluate the treatment under different delivery scenarios.

Results

Modelling predictions demonstrate the advantages of the combination using focused ultrasound and nano-drug carriers in improving the delivery outcomes. This improvement can also be enlarged in different ways, including the sonication timing and duration, as well as the nanoparticle design. More free drugs can enter the tumour tissue when the burst sonication starts simultaneously with the drug administration. Prolonging the sonication duration is effective to lead to more effective drug release from nanoparticles in the tumour. Moreover, the drug release rate needs to be optimised in order to keep the trade-off between the release dynamics, transvascular exchange and drug elimination.

Discussion

Because of the fast recovery of BBB disruption to nanoparticles, burst sonication has a very limited impact on the transvascular transport of nanoparticles. Further analyses show that this improvement is largely due to the enhanced transvascular transport of released free drugs and sustainable drug supply. This highlights the importance to prolong the sonication duration for better treatment. Furthermore, the BBB disruption by focused ultrasound is also subject to multiple factors including microbubbles, power and frequency of ultrasound, etc. A parameter study could be useful to understand the effects of each factor.

Conclusions

The results obtained in this study can serve as a reference for the design of the combination therapy against brain tumour using focused ultrasound and nanoparticles.

References

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Brain tumour; Blood-brain Barrier; Drug transport; Focused ultrasound; Mathematical model