Ultrasound Programmable Hydrogen-Bonded Organic Frameworks for Sono-Chemogenetics

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Abstract

Introduction: The precise control of mechanochemical activation within deep tissues using non-invasive ultrasound holds profound implications for advancing our understanding of fundamental biomedical sciences and revolutionizing disease treatments. However, a theory-guided mechanoresponsive materials system with well-defined ultrasound activation has yet to be explored. Here we present the concept of using porous hydrogen-bonded organic frameworks (HOFs) as toolkits for focused ultrasound (FUS) programmably triggered drug activation to control specific cellular events in the deep brain.

Method: We have developed HOFs that could be precisely tailored and selectively activated through non-invasive ultrasound to facilitate remote medication manipulation, offering precise disease treatment in deep tissues. A theoretical model is developed to visualize the mechanochemical scission and ultrasound mechanics, providing valuable guidelines for the rational design of mechanoresponsive materials to achieve programmable control. To demonstrate the practicality of this approach, we encapsulate the designer drug clozapine N-oxide (CNO) into the optimal HOF nanocrystals for FUS-gated release to activate engineered G-protein-coupled receptors in the ventral tegmental area (VTA) of mice and rats and hence achieve targeted neural circuit modulation even at depth 9mm with a latency of seconds.

Result: This work presents an ultrasound-activated HOF system with finely tuned interactions at the molecular level through modifying the chemical structure of interaction units. Through the manipulation of hydrogen bond density and the number of aromatic fused rings in the backbone structures of the organic ligands, a theoretical model is developed to explain the structure and functionality relationships in the HOFs, providing valuable guidelines for the precise and rational design of HOF building units at the molecular level to achieve on-demand and programmable drug activation under a desirable ultrasound pressure. By tuning HOF nanocrystals sensitivity to respond to focused ultrasoudn (FUS), we successfully achieve spatiotemporal control of deep brain neural circuits in both mice and rats with a latency of only seconds. The results demonstrate that HOF-enabled sono-chemogenetics can achieve a high temporal resolution and long-period neuromodulation while retaining the benefits of minimal invasiveness.

Discussion: Our sono-chemogenetics technology is advancing toward applications in non-human primates and human disease treatment. While the current delivery of viruses and nanocrystals relies on local injection, FUS-mediated blood-brain barrier opening could reduce invasiveness, paving the way for future clinical applications of sono-chemogenetics.

Conclusions: Our findings have demonstrated that our Ultrasound-activated HOF technology has the combination of high drug-loading content, high biostability, low immunogenicity and unique ultrasound programmability for non-invasive, precise medication therapy. Our technology is capable of releasing different types of molecule with designable medication activation sensitivity and resolution.

References

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