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Novel Glycine Receptor Modulators for Analgesia ID: 04250

Featured Innovators: Yan Xu, PhD and Pei Tang, PhD

About a quarter of patients who receive prescription opioids for long-term pain struggle with addiction, and overdose deaths involving prescription opioids have quadrupled since 1999. THC – the main chemical component of marijuana – has gained popularity as an alternative analgesic for treating chronic pain, but psychoactive side effects and political controversy have stymied widespread adoption. Our new class of compounds avoids these issues by capturing only the pain relief aspect of THC, potentially reducing the need for opioids.

Technology Description

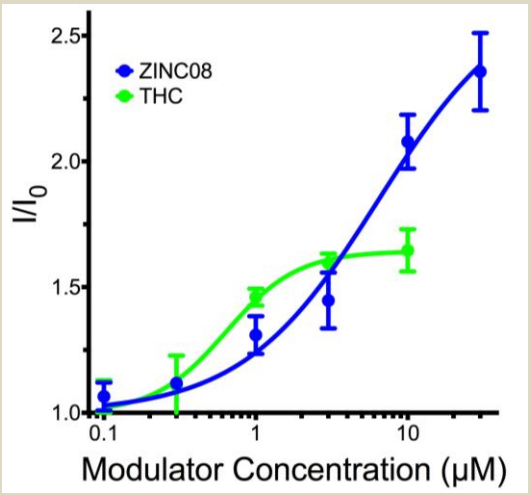
Recognizing that glycine receptors are responsible for the analgesic effects of marijuana, we screened a library of drug-like molecules for structural compatibility with the same glycine receptor binding site as THC. A representative compound from this group – ZINC08 – was even more effective than THC at enhancing human glycine receptor function *in vitro*. In mouse behavioral tests, ZINC08 reduced the effects of inflammatory pain and boosted the efficacy of a sub-therapeutic dose of morphine. Patients and prescribers could use ZINC08 and other glycine receptor modulators in its class to reduce the necessary dose of opioids for pain management, eliminating side effects such as dependence, tolerance, addiction, sedation, and nausea.

Advantages

- Captures only the analgesic effects of THC
- Does not affect normal sensitivity to pain under non-inflammatory conditions
- Synergistic with morphine

Applications

- Treating hypersensitivity to inflammatory pain
- Treating pain from surgery, tissue damage, infection, neuropathic conditions , or skeletal muscular conditions
- Reducing the necessary dose of opioids for chronic pain management
- Prophylactic pain relief (e.g., to prevent surgical pain or anticipated opioid withdrawal pain)



ZINC08, a representative of our new class of glycine receptor modulators, is more effective than THC at enhancing the function of human glycine receptors.

Stage of Development

In vitro and *in vivo* behavioral data

IP Status

Provisional patent application filed

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Innovators

Yan Xu, PhD

Peter Winter Professor of Anesthesiology

Professor of Pharmacology & Chemical Biology, Physics & Astronomy, and Structural Biology

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Department of Anesthesiology
University of Pittsburgh

The research in Dr. Xu's laboratory focuses on receptor engineering as a new class of drugs for the treatment of chronic pain, rational design of new therapeutic strategies to treat neuronal injuries during and after cerebral global ischemia, and the molecular and cellular mechanisms underlying the actions of low-affinity neurological drugs. In the first project, recent activities have been directed towards developing targeted delivery of engineered ion channels to nociceptors to treat chronic pain. In the second project, systemic immune modulation and its coupling with the central nervous system are investigated to develop new therapies for repercussion injuries. The third project involves the 3-D structure and dynamics measurements of ion channel receptors. Dr. Xu is also interested in the molecular and cellular basis of consciousness.

Education

PhD in Physical Chemistry
State University of New York, Stony Brook

MS in Physical Chemistry
University of Science and Technology of China

BS in Physics
University of Science and Technology of China

Pei Tang, PhD

Professor
Anesthesiology, Pharmacology, & Chemical Biology
Computational and Systems Biology
University of Pittsburgh

Dr. Tang is interested in the action of low-affinity drugs – such as general anesthetics and alcohols – on neurotransmitter-gated receptor channels. Her current research focuses on the structures, dynamics, and functions of neuronal nicotinic acetylcholine receptors (nAChRs), γ-aminobutyric acid receptors (GABAA), and their bacterial homologues (ELIC and GLIC). She has developed various expression systems for the over-production of channel proteins in such a large quantity and high purity that they can be studied by high-resolution nuclear magnetic resonance (NMR), spectroscopy, and X-ray crystallography. Parallel to her experimental approaches, she is also developing theoretical models to generalize the underlying mechanisms of low-affinity drug interaction with ion channel proteins. Her long-term goal is to uncover the structure-function and dynamics-function relationships of drug action at or near atomic resolution.

Education

PhD in Physical Chemistry
State University of New York, Stony Brook

BS in Chemistry
University of Science and Technology of China

Publications

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- Xiong W, Cheng K, Cui T, Godlewski G, Rice KC, Xu Y, Zhang L. Cannabinoid potentiation of glycine receptors contributes to cannabis-induced analgesia. Nature Chemical Biology. 2011 May 1;7(5):296-303.
- Wells MM, Reinert N, Tang P, Xu Y. Structure-Based Discovery of Novel Glycinergic Modulators. Biophysical Journal. 2017 Feb 3;112(3):556a.
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