Researchers uncover molecular mechanism of methamphetamine binding to trace amine receptor

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Methamphetamine (meth) abuse is a major health concern. Understanding how meth interacts with its target proteins is crucial for

the development of novel medications to address drug addiction. Previous research into the mechanism of meth's effects has mainly focused on the dopamine system, but recent studies suggest it may also directly bind to the trace amine receptor 1 (TAAR1), which plays a key role in psychostimulant abuse-related behaviors.

TAAR1 is a receptor in the brain that recognizes various biogenic amines, including the natural compound β-phenethylamine (β-PEA). TAAR1 agonists have been proven effective in treating a range of diseases, including schizophrenia, depression, bipolar disorder, and drug addiction, due to the pivotal role of TAAR1 in modulating monoaminergic systems. Therefore, studying the interactions between meth and TAAR1 through structural biology may aid in addiction treatment and new antipsychotic drug development.

In a study published in *Nature*, a team of researchers led by H. Eric Xu from the Shanghai Institute of Materia Medica of the Chinese Academy of Sciences (CAS), in collaboration with Xu Fei from the iHuman Institute at ShanghaiTech University, Wang Sheng from the Center for Excellence in Molecular Cell Science of CAS, and their collaborators, has uncovered the molecular mechanism of meth binding to the trace amine receptor TAAR1.

Meth, or crystal meth, was once used for medical purposes but is now abused. It is similar to drugs such as morphine and fentanyl which have their own clinical applications but carry risks of abuse and addiction. To ensure safe and controlled use is important.

Prof. H. Eric Xu's team has conducted scientific research on critical issues associated with drug addiction. For example, his team has published two *Cell* papers, which have systematically elucidated the mechanisms of interaction between opioid receptors and various small molecule analgesics and endogenous opioids, particularly fentanyl,

providing a solid basis for pharmacological intervention in analgesia, addiction and mood regulation by targeting opioid receptors.

In this new study, the researchers used cryo-electron microscopy (cryo-EM) to determine high-resolution structures of the human TAAR1-Gs protein complex stimulated by meth, β-PEA, the selective agonist RO5256390, and the clinical candidate SEP-363856. Structural analysis revealed that meth binds to TAAR1 mainly through polar interactions with Asp103 and Tyr294. A hydrogen bond network around the binding site stabilizes meth–TAAR1 interactions.

In addition, the extracellular loop 2 (ECL2) of TAAR1 forms a unique "lid" that interacts with the ligands, using Phe186 and other hydrophobic residues. Compared to β-PEA, meth forms weaker polar interactions with Asp103 and Ser107, which explains why β-PEA has a higher binding affinity to TAAR1.

In addition, the structural pharmacology of clinical candidate SEP-363856 (a dual $5HT_{1A}R$ and TAAR1 agonist) and the selective TAAR1 agonist RO5256390 bound to TAAR1 was explored. Structural analysis and mutagenesis experiments revealed how these compounds interact with the receptor and why they exhibit different selectivity and affinity.

For example, the common interactions that govern the recognition of SEP-363856 by TAAR1 or $5\text{-}HT_{1A}R$ may provide the structural foundation for the polypharmacology of SEP-363856. RO5256390, on the other hand, has additional interactions with TAAR1, providing selectivity over $5\text{-}HT_{1A}$ due to steric hindrance.

This study provides the long-awaited structure of a monoaminergic receptor targeting by meth, thus laying a foundation for the development of new addiction treatments and drugs for psychiatric disorders. The

structural elements governing TAAR1 recognition by meth and other amines elucidated in this study will benefit future pharmacological studies and the development of next-generation drugs.

More information: Heng Liu et al, Recognition of methamphetamine and other amines by trace amine receptor TAAR1, *Nature* (2023). DOI: 10.1038/s41586-023-06775-1

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