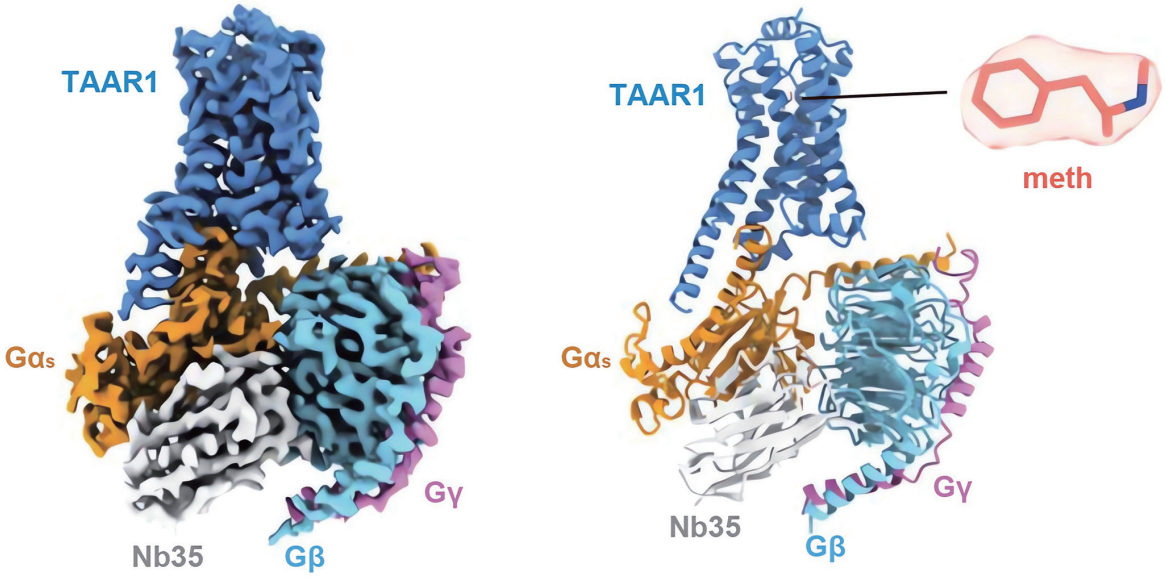
Unlocking the Brain's Gateway to Methamphetamine Addiction

By YAN Fusheng

What secret molecular key enables methamphetamine, or meth for short, to ruthlessly hijack the brain's reward system, leading countless individuals down spiral paths of addiction? Thanks to innovative research reported this month in *Nature*, we finally have critical clues.



Scientists reveal how meth activates its key target receptor TAAR1, a gateway receptor for trace amines, in the brain. (Credit: SIMM)

A recent study published in *Nature* on November 7 offers new clues into understanding and potentially treating meth addiction, one of society's most damaging substance abuse disorders.

A team of researchers led by Dr. XU Huaqiang from the Shanghai Institute of Materia Medica (SIMM) of the Chinese Academy of Sciences (CAS), in collaboration with Dr. XU Fei from the iHuman Institute at ShanghaiTech University, Dr. WANG Sheng from the Center for Excellence in Molecular Cell Science of CAS, and their collaborators, have discovered the precise molecular mechanism by which meth activates its key target receptor in the brain, leading to the euphoric highs.

The study reveals how meth binds to and triggers the trace amine associated receptor 1 (TAAR1) to induce sensations of pleasure and contentment. Using advanced structural biology techniques, the scientists visualized the intricate molecular dance of TAAR1 responding to meth. These atomic-level insights could pave the way for developing new addiction treatments that sabotage this interaction.

The new research builds on prior work identifying TAAR1's integral involvement in meth addiction. TAAR1 functions as a gateway receptor for trace amines, a class of naturally occurring compounds with chemical similarities to meth. When activated, TAAR1 triggers downstream release of the "feel-good" neurotransmitter dopamine, which underlies rewarding experiences ranging from enjoying food to falling in love. Meth, however, unleashes a flooding tsunami of dopamine instead of a gentle wave, resulting in a sense of euphoria that leaves users compulsively chasing the next high.

Shutting down TAAR1 offers promise for treating addiction, but designing targeted drugs first required demystifying how meth interacted with it on a molecular level.

Leveraging single particle cryo-electron microscopy (cryo-EM) to snap atomic-scale molecular selfies of TAAR1 responding to meth, the team unveiled TAAR1's activation mechanism in meticulous detail, akin to possessing the blueprint guiding how meth picks the receptor's lock.

The results show that meth elegantly mimics TAAR1's native ligands but with greater precision and potency – no wonder the downstream dopamine flood drives such intense highs.

Armed with these structural insights, researchers can now pursue smart drug design to interfere with this molecular tango between meth and its gateway receptor. Potential avenues include decoy compounds that compete with meth for TAAR1 binding, rendering the receptor inert to further meth stimulation. Researchers also spotted a molecular lid that can latch and shut over the binding pocket region, sealing out meth while avoiding natural ligands that remain important for normal nerve signaling.

Beyond advancing treatment options, the research also sheds light on why some individuals may be biologically prone to meth addiction. Subtle differences in TAAR1's molecular contours that enhance binding affinity for meth likely make certain people more vulnerable.

Overall, while much work remains before new therapies reach clinical trials, the team is energized by the prospects their foundational study enables. It is good to see that innovative insights into protein structures at nanoscales may have the power to turn the table of battling societal scourges like meth addiction.

Reference

Liu, H., Zheng, Y., Wang, Y., Wang, Y., He, X., Xu, P., . . . Xu, F. (2023). Recognition of methamphetamine and other amines by trace amine receptor TAAR1. *Nature*. doi:10.1038/s41586-023-06775-1