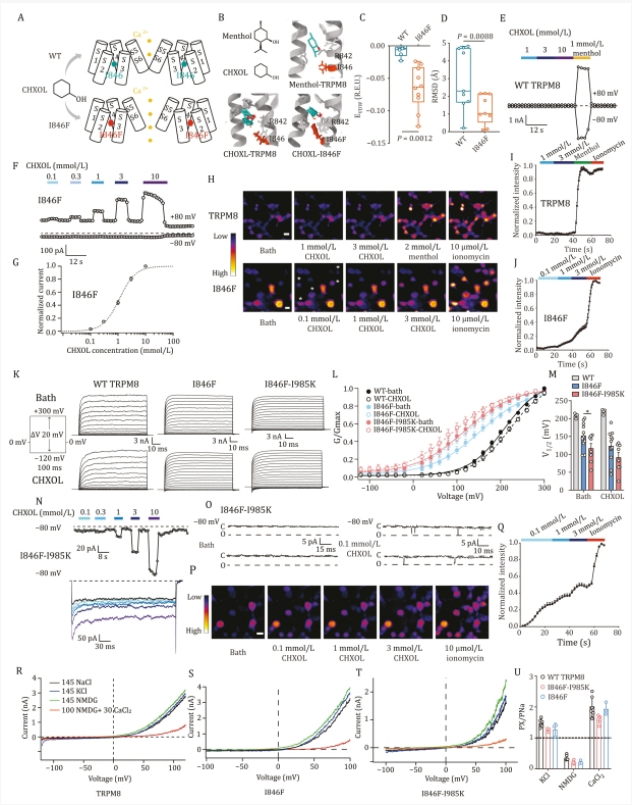
Engineered ion channel offers precise, non-invasive control of brain activity

FAYETTEVILLE, GA, UNITED STATES, May 30, 2025 /EINPresswire.com/ -- In a breakthrough advancement for neuroscience, researchers have developed RADICAL, a cutting-edge chemogenetic tool that allows for the precise manipulation of neuronal activity using a synthetic chemical, cyclohexanol (CHXOL). Unlike traditional methods that rely on invasive optics or slow-acting G-protein coupled receptors, RADICAL utilizes a modified TRPM8 ion channel to enable rapid and targeted control of calcium influx in neurons. This innovative tool has the potential to advance brain function research and open up new therapeutic possibilities for neurological disorders.



Engineering of TRPM8 channel to be activated by CHXOL and more sensitive to CHXOL.

Current technologies for controlling neuronal activity—such as optogenetics and chemogenetics—have their limitations. Optogenetics requires invasive light delivery, while chemogenetic systems like DREADDs rely on slow and indirect cellular signaling pathways. Additionally, engineered ligand-gated ion channels, such as those based on nicotinic receptors, can result in unintended interactions with native proteins. These challenges have highlighted the need for a more efficient, non-invasive, and precise method of modulating neuronal excitability. In response to this gap, researchers sought to develop RADICAL, a novel chemogenetic tool that addresses these limitations.

In a letter (DOI: 10.1093/procel/pwae048) published on September 3, 2024, in Protein & Cell, a team from Zhejiang University unveiled RADICAL, an engineered ion channel activated by cyclohexanol (CHXOL). By introducing specific mutations to the TRPM8 ion channel, they created a system that responds with exceptional sensitivity and specificity to CHXOL. This innovation allows for precise neuronal control without interfering with the brain's native functions, marking a significant step forward in chemogenetics.

The key modification in RADICAL was the engineering of the TRPM8 ion channel, which is naturally expressed at low levels in the brain, minimizing potential disruptions to endogenous systems. The team introduced two critical mutations (I846F and I985K) to the TRPM8 ion channel. The I846F mutation restored CHXOL binding, while I985K enhanced voltage sensitivity, enabling robust activation even at hyperpolarizing potentials (-80 mV). Patch-clamp recordings and calcium imaging confirmed the double mutant, TRPM8-I846F-I985K's EC50 of 1.17 mmol/L for CHXOL at depolarizing potentials (+80 mV). In vivo, RADICAL demonstrated its potential: CHXOL administration enhanced fear extinction memory in mice by activating neurons in the infralimbic cortex (IL), and also increased locomotor activity when expressed in astrocytes of the ventral tegmental area (VTA). Importantly, the tool's calcium permeability and minimal cell death risk, as shown in HEK293T cells, suggest its suitability for studying calcium-dependent processes such as learning and memory.

Dr. Fan Yang, one of the co-corresponding authors of the study, said: RADICAL represents a major breakthrough in chemogenetics. Its ability to modulate neuronal activity with high precision and minimal off-target effects makes it a versatile tool for both basic neuroscience research and the development of therapeutic interventions.

With its non-invasive approach and high specificity, RADICAL has substantial potential in both research and clinical settings. It could enhance our understanding of neurological conditions such as memory disorders, addiction, and mood disorders by providing a precise way to manipulate neuronal circuits. Furthermore, future efforts to miniaturize the tool for adeno-associated virus (AAV) delivery could broaden its applicability in gene therapy. RADICAL's unique combination of speed, specificity, and safety positions it as a powerful platform for next-generation treatments of brain diseases.

References

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