NEUROSCIENCE

Potent chemogenetics

An optimized chemogenetic tool enables highly specific and potent neuronal manipulations.

One way to manipulate the activity of neurons is via chemogenetics. This technology involves a designed receptor that is essentially inert unless a specific ligand is administered, thereby opening an ion channel moiety in the receptor and perturbing neuronal activity. Chemogenetics is a popular approach in basic research, but there is potential for clinical applications, for example, in the treatment of neurological disorders that are localized to particular brain areas.

Scott Sternson from the Janelia Research Campus in Ashburn, Virginia, wanted “to develop a chemogenetic receptor that had potency for an existing clinically approved drug that was well behaved and got into the brain and was well tolerated.” In close collaboration with scientists from the National Institute on Drug Abuse, New York University, and Emory University, Sternson

and his team screened a panel of approved drugs for agonist (meaning activating) activity toward the PSEM chemogenetic receptor, and found the anti-smoking drug varenicline to be a potent agonist. They further modified the ligand-binding region of PSEM to increase its potency and reduce binding by endogenous ligands. The combination of varenicline and the modified PSEM constitutes a highly potent chemogenetic system that can potentially be applied in humans, as varenicline is already an approved drug.

For basic research applications, Sternson and his team further optimized the system. “My background before I moved to neuroscience was in synthetic chemistry, and I thought that the chemical agonist part of chemogenetics had not been as thoroughly optimized as the receptors have,” says Sternson. Hence, Sternson and his

team generated derivatives of varenicline that are even more potent than varenicline and that have fewer effects on endogenous acetylcholine receptors, which are the target of varenicline. Sternson considers the chemogenetic system they developed to be dual-use. “We would recommend for research purposes to use the most selective molecules,” explains Sternson, while varenicline could be used in applications with translational potential, as the drug is already clinically approved.

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Research papers
 Magnus, C. J. et al. Ultrapotent chemogenetics for research and potential clinical applications. *Science*
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