New avenues to developing personalized treatments for schizophrenia

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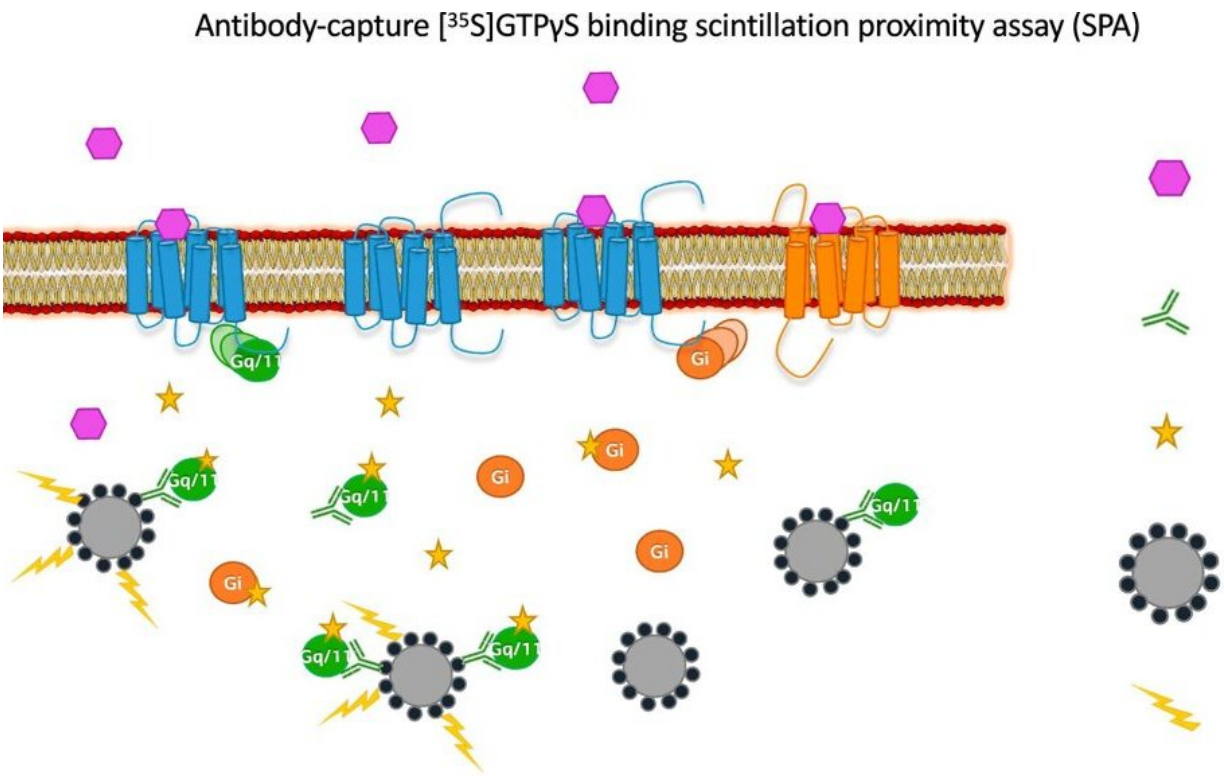

Antibody-capture [^{35}S]GTPγS binding scintillation proximity assay (SPA). Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-48196-2

An international study, published in *Nature Communications*, may facilitate the creation of new personalized treatments for people diagnosed with schizophrenia. These are patients who suffer from various types of symptoms, such as delusions, hallucinations, cognitive deficits, memory or language impairment, and depressive symptoms.

Current treatments, largely targeting a specific therapeutic target, the type 2A serotonin receptor, do not allow for selective action on the symptoms experienced by the patient, causing side effects, and metabolic or motor issues, among others, that lead to treatment abandonment.

In this context, the study has identified the role of certain proteins, the G proteins, which play a vital role in modulating cell responses in schizophrenia. Specifically, it was shown that two types of these proteins allow for the modulation of the main symptoms of this disorder.

The research was led by the Hospital del Mar Medical Research Institute, in collaboration with researchers from the Neuropsychopharmacology Group at the University of the Basque Country (UPV/EHU) and researchers from the CIBER of Mental Health (CIBERSAM).

Dr. Jana Selent, one of the principal authors of the study and coordinator of the Drug Discovery Group based on G protein-coupled receptors at the Hospital del Mar Medical Research Institute, says, "These proteins are coupled to the same receptor, but they do not act in the same way, causing diverse reactions in the cells, which provides us with very valuable information for future studies that will enable the development of drugs for the treatment of schizophrenia in a personalized manner, tailored to each patient's symptoms."

High complexity study

To reach these conclusions, the researchers had to conduct complex research. The starting point was to select various available molecules, although they are not approved drugs for humans, to analyze at a molecular level and through atomic-level simulations, their ability to interact with the type 2A serotonin receptor. This allowed the selection of four compounds, which were first studied in cells, where it was demonstrated that upon binding to the receptor, they triggered responses in different types of G proteins.

These results were applied to analyses in human brain tissue samples from the Neuropsychopharmacology Group's collection at the University of the Basque Country (UPV/EHU). In these studies, it was observed that "the compounds had very different activity concerning the G proteins: some activated them, but others deactivated them," explains Dr. Patricia Robledo, also a principal author of the study and researcher at the Integrated Pharmacology and Systems Neuroscience Group.

In this regard, "the possibility of inhibiting the coupling of the serotonin 2A receptor to certain G proteins has been proposed as an area of interest for designing a new type of drug, known as inverse agonists, as potential tools against psychotic conditions," notes Rebeca Diez-Alarcia, first co-author of the article and researcher at UPV/EHU.

Moreover, in a mouse model designed to simulate schizophrenia symptoms, these compounds had specific behavioral effects depending on which G protein they activated. Thus, using pharmacological and genetic techniques in mice, it was found that one of these G proteins is involved in symptoms related to psychosis, and another type of G protein with cognitive deficits.

Dr. Robledo says, "This is the first time that promising therapeutic

targets have been identified for developing drugs that act and benefit a specific profile of schizophrenia patients."

Although the compounds used in the study are not yet approved drugs for human use, Dr. Jana Selent says that "this multi-scale work reveals a plan for the chemical design of future drugs that address more specific pathways to treat schizophrenia, avoiding pathways associated with side effects, which is of great relevance for a more personalized treatment."

Dr. Daniel Berge, a psychiatrist at the Mental Health Institute of the Hospital, who did not participate in the work, points out that "this study will help design more selective drugs for the treatment of schizophrenia, which can offer better tolerance and higher precision on the symptoms of the disease. All this would promote better treatment adherence, which is key to preventing relapses and achieving a better quality of life."

More information: Elk Kossatz et al, G protein-specific mechanisms in the serotonin 5-HT2A receptor regulate psychosis-related effects and memory deficits, *Nature Communications* (2024). DOI: 10.1038/s41467-024-48196-2

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