Scientists caution use of a novel technique to understand relationship between brain activity & behavior

Scientists at Jawaharlal Nehru Center for Advanced Scientific Research (JNCASR), Bengaluru, have found a gap in new technology that is today widely used to study communication between neurons.

Dr. James Clement's lab at JNCASR, Bengaluru, along with Prof Vidita Vaidya's lab (Main author) at Tata Institute of Fundamental Research (TIFR), Mumbai, demonstrated specific flaws in Chemogenetics which is a technique that uses chemicals to understand how neurons are activated. Chemogenetics is the process by which macromolecules can be engineered to interact with previously unrecognized small molecules and has been widely used to understand the relationship between brain activity and behavior.

The team of scientists found that the chemogenetics process initiates a plethora of downstream signalling pathway and cannot be merely a substitution to study the neuronal activity and function. It manipulates genes to place the neurons under the control of special receptors called DREADD - Designer Receptors Activated by Designer Drugs – that only bind to an inert chemical called Clozapine-N-Oxide (CNO). Hence it should be used with caution. The study funded by the Department of Science and Technology and Scientific and Engineering Research Board was published in the journal eNeuro, 2019.

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DREADD-based technology to study neuronal function has been used for almost a decade, but it is unclear how activation of DREADD by different concentrations of CNO the inert chemical, can affect neuronal activity. The researchers used a designer receptor named hM3Dq for their study. When this receptor interacts with CNO, it increases calcium ions within the cell, which then induce the release of chemical messengers called neurotransmitters. However, it is not clear what dosage of CNO is optimal to activate DREADD alone without having a secondary impact on neuronal function.

Their study is the first to caution the use of DREADD to understand the neuronal activity and highlight the flaws in this technique using whole-cell patch-clamp and extracellular field recordings from the mouse hippocampal brain region.

Through this study, the team has found that the application of different dosages of CNO had widespread effects on neurons. The reason for these different effects could be a consequence of the activation of various signalling pathways as the CNO concentration increases and the way it is metabolised. They found out that a low dose of CNO increased the chances of neuronal activation, and a high dose led to a reduction in neuronal excitability. Their data demonstrate that DREADD should be used with caution as it initiates a plethora of downstream signalling pathway and cannot be merely a substitution to study the neuronal activity and function.

Electrophysiology is the fundamental technique essential to study the neuronal function (communication between neurons). Using this technology, Dr. James Clement and his team were able to dissect the mechanism of the impact of different doses of CNO induced activation of DREADD on neuronal function. Besides, DREADD is an emerging technology to precisely control neuronal activation, which enables the researchers to study a specific signalling pathway in a given population of a neuron. Thus, DREADD gives researchers a better control on which group of neurons are activated and enables researchers to find precise mechanisms of neuronal activity and function. Using the pioneering technique of electrophysiology, they have demonstrated that DREADD and CNO should be used with caution to study neuronal function.

Prof Vidita Vaidya's lab at TIFR observed discrepancy in behavioural experiments when the varied concentration of CNO was applied on DREADD mice. This finding led to probe whether altering the concertation of CNO (or differential activation of DREADD) results in various neuronal activation and, thus, the differential neuronal function, which was reflected in the behaviour. During the discussion with Dr. James Clement, they decided to pursue these questions that led to the study published in eNeuro.

The 1st author of the study, Dr. Sthitapranjya, from Prof Vidita's lab, spent more than a year in Dr. James' lab at JNCASR to perform extracellular field recordings and whole-cell patch-clamp experiments from brain slices of genetically modified mice where the designer receptors were present on the primary excitatory neurons of the Schaffer Collateral pathway, which is essential for memory formation and controlling them by chemogenetics revealed a lot about their functions.

The findings of the study would be useful for researchers working to develop the next generation chemogenetic tools as they can design ways to remedy these shortcomings and variability of the engineered receptors. These tools can be used to understand how specific brain regions are more affected in disease models like in neuro-developmental disorders such as Autism Spectrum Disorder, and psychiatric disorders like depression or anxiety.