Brain signaling proteins hit the road running

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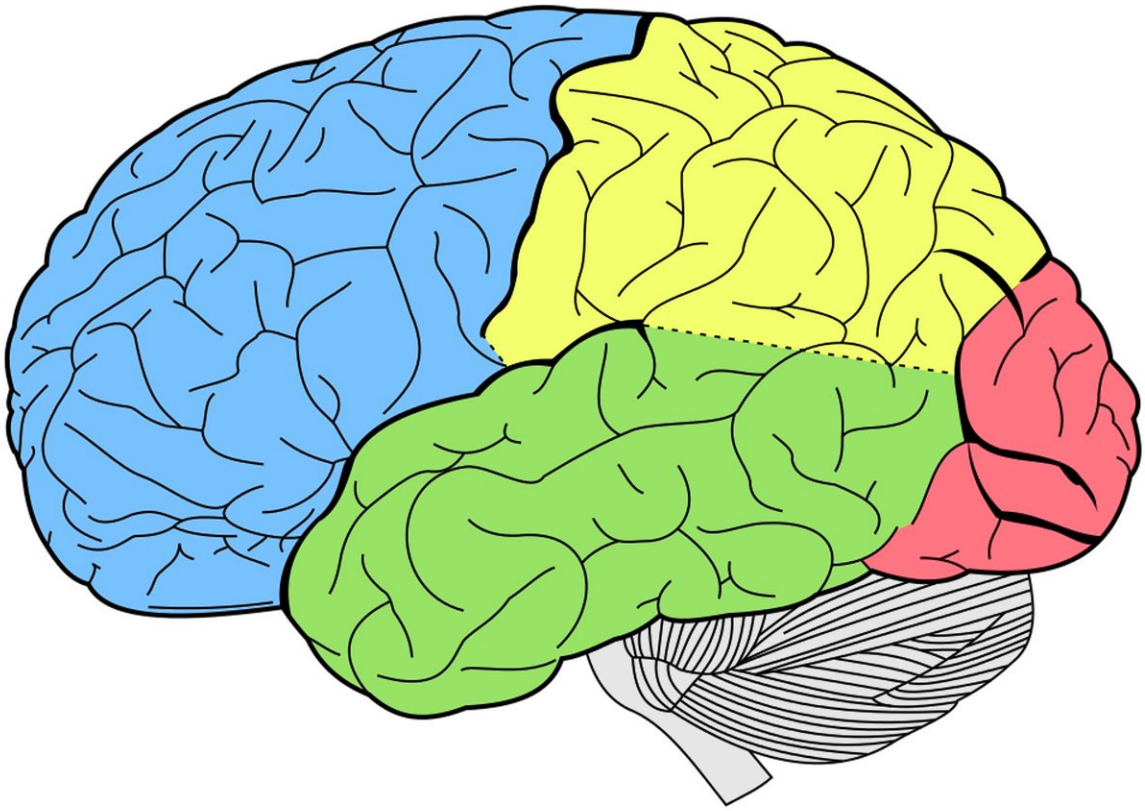

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Surprisingly complex movements in an important neurotransmitter receptor may help explain the brain's unpredictable response to drugs, according to a new study. New research from an international team, published this week in the journal *Neuron*, has revealed that the resting

state of signaling proteins are much more dynamic than previously thought.

In the brain, most drug targets consist of signaling proteins that go awry in central nervous system diseases, for example with autism in childhood, schizophrenia in adolescence, or Alzheimer's disease in old age. The aim of drug treatment is to correct the inappropriate behavior of these proteins and restore normal brain function.

Correctly identifying drug targets is a major challenge for modern medicine. Although a lot of time, effort and money has been dedicated to the development of drugs for neurological disease over the years, the failure rate has been significant. "One of the main reasons for failure is due to the lack of drug efficacy and off-target effects," explains Dr. Derek Bowie, Professor in the Department of Pharmacology and Therapeutics at McGill University's Faculty of Medicine, and one of the paper's senior authors. "These outcomes, in particular, have put into question the validity of strategies used by pharmacologists to identify and target signaling proteins. An understated concern is that the basic tenets of drug targeting may be flawed."

An exciting but unexpected discovery

Through a collaborative effort consisting of scientists from McGill, the University of Cambridge, the University of Copenhagen and Pontificia Universidad Católica de Chile, the researchers uncovered an important property of the ionotropic glutamate receptor (iGluR) protein, which they believe will have important ramifications for biomedical research as well as for future drug development.

Though traditionally drug developers have targeted proteins in an active state, the researchers found that iGluRs in a resting state are highly mobile and dynamic, which profoundly affects how they respond to

drugs. "Importantly, this behaviour is regulated by our genes which act as a master-switch to turn the effect of the drug on or to switch it off completely," says Prof. Bowie.

A major drug target for decades, despite their importance, few drugs targeting iGluRs have reached the clinic for the treatment of neurological disease. "Our recent findings introduce a new complexity into our understanding of iGluRs, which may explain previous disappointments while also shedding light on how to best move forward," adds Bowie.

A series of fortunate events

The discovery came about serendipitously, spawning from an unplanned discussion between Bowie and Dr. Jette Sandholm Kastrup in Copenhagen in 2013. "Our collaboration was initiated at a Benzon Symposium in Copenhagen when Dr. Bowie and I discussed the idea that AMPA receptors—the most common type of receptors found in the nervous system—might be modulated by anions," says Dr. Kastrup, Professor at the University of Copenhagen and one of the study's senior authors. "At that time we did not imagine that this collaboration would extend to combine efforts of four universities. Our work, using X-ray crystallography, allowed us to locate the anion binding site in the atomic structure of the AMPA receptor."

Dr. Kastrup thought that this new crystallized AMPA-type ionotropic glutamate receptor her lab had developed could help shed light on an observation Dr. Bowie had made in 2002. Upon his return to McGill, Dr. Bowie's lab used the crystallized structure to help identify that a single amino acid was responsible for determining whether different genetic isoforms of the same AMPA receptor could be either fully regulated or not regulated at all.

The next important breakthrough then came, again by chance, when Dr. Bowie visited Cambridge in 2015 and met with Dr. Mike Edwardson, who had been working with Dr. Nelson Barrera from the Pontificia Universidad Católica de Chile to use atomic force microscopy to study protein movement in real time. Dr. Bowie shared some of the unpublished data and Dr. Edwardson agreed to run a few experiments. "To our surprise, we found that the key amino acid that conferred different properties on the same AMPA receptor was due to changes in the (nanoscale) mobility or movement of the protein's resting or apo state," explains Dr. Edwardson, the Sheild Professor of Pharmacology at the University of Cambridge and senior author on the paper.

The impact of the findings have broad appeal to many other signaling proteins inside and outside of the brain. Consequently, the study uncovers an important aspect of biology that may need to be considered when developing drugs in the future. "I cannot stress how unexpected this finding was to us since most of the field had overlooked that the resting protein can have complex dynamics," notes Dr. Bowie. "This oversight can also be extended to almost all biomedical research on signaling proteins where the underlying assumption has been that only the active form of the protein is worthwhile studying and not the resting or apo state. Our recent study shows that assumption needs to be revised, which opens up an entirely new area of study that could have impact on other areas of investigation such as in cancer, heart disease in addition to our findings on an important brain neurotransmitter receptor. "

More information: G. Brent Dawe et al, Nanoscale Mobility of the Apo State and TARP Stoichiometry Dictate the Gating Behavior of Alternatively Spliced AMPA Receptors, *Neuron* (2019). DOI: 10.1016/j.neuron.2019.03.046

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