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Scientists investigate initial molecular mechanism that triggers neuronal firing

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Carnegie Mellon University chemists have solved a decade-long molecular mystery that could eventually help scientists develop drug therapies to treat a variety of disorders, including epilepsy and Alzheimer's disease.

Using intensive theoretical and computational calculations, Carnegie Mellon researchers have modeled the initial molecular changes that occur when the neurotransmitter glutamate docks with a receptor on a neuron, which sets in motion a chain of events that culminates in the neuron firing an electrical impulse.

Tatyana Mamonova, a postdoctoral fellow in Assistant Professor Maria Kurnikova's laboratory at Carnegie Mellon, will present this report Wednesday, Aug. 22 at the 234th national meeting of the American Chemical Society in Boston.

Glutamate receptors, which are proteins found in neurons, form a channel through the neuron's membrane. When glutamate, a signaling molecule released by other neurons, docks with the glutamate receptor, it causes a series of molecular shape changes that eventually open the channel and excite the neuron. Although the structure of the glutamate receptor's docking site was known, no one knew precisely which atomic interactions between glutamate and the receptor caused the receptor to change its conformation — until now.

"The docking site (or ligand binding domain) closes when glutamate

binds to it. Tatyana found two key electrostatic interactions that lock the ligand-binding site in its closed form once the ligand is bound," said Kurnikova. "With this knowledge in hand, we can now model binding-site closure and opening using a computer."

Being able to simulate this conformational change is critical to understanding how binding regulates the protein channel, Kurnikova added. "Ultimately, we could use the computer model to design a drug that either inhibits or enhances the activity of the glutamate receptor. Typically, pharmaceutical companies may scan hundreds of potential drugs to find one that has the desired affect. Determining how drugs interact with the glutamate receptor's ligand-binding domain in a computer model would save tremendous time and money in the drug-development process."

To pinpoint the molecular mechanism that switches the binding domain's conformation from open to closed, Mamonova used a variety of chemical-modeling techniques, including molecular dynamics simulations, continuum electrostatics studies, and rigidity and hydrogen-bond analyses. Many of these tasks are theoretically and computationally intensive, and Mamonova frequently relied on the high-performance computing power at the Pittsburgh Supercomputing Center, a joint effort of Carnegie Mellon and the University of Pittsburgh together with Westinghouse Electric Company.

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Source: Carnegie Mellon University