Research gives new insight into how antidepressants work in the brain

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(Medical Xpress)—Research from Oregon Health & Science University's Vollum Institute, published in the current issue of *Nature*, is giving scientists a never-before-seen view of how nerve cells communicate with each other. That new view can give scientists a better understanding of how antidepressants work in the human brain—and could lead to the development of better antidepressants with few or no side effects.

The article in today's edition of *Nature* came from the lab of Eric Gouaux, Ph.D., a senior scientist at OHSU's Vollum Institute and a Howard Hughes Medical Institute Investigator. The article describes research that gives a better view of the structural biology of a protein that controls communication between nerve cells. The view is obtained through special structural and biochemical methods Gouaux uses to investigate these neural proteins.

The *Nature* article focuses on the structure of the dopamine transporter, which helps regulate dopamine levels in the brain. Dopamine is an essential neurotransmitter for the human body's central nervous system; abnormal levels of dopamine are present in a range of neurological disorders, including Parkinson's disease, drug addiction, depression and schizophrenia. Along with dopamine, the neurotransmitters noradrenaline and serotonin are transported by related transporters, which can be studied with greater accuracy based on the dopamine transporter structure.

The Gouaux lab's more detailed view of the dopamine transporter structure better reveals how anti-depressants act on the transporters and thus do their work.

The more detailed view could help scientists and pharmaceutical companies develop drugs that do a much better job of targeting what they're trying to target—and not create side effects caused by a broader blast at the brain proteins.

"By learning as much as possible about the structure of the transporter and its complexes with antidepressants, we have laid the foundation for the design of new molecules with better therapeutic profiles and, hopefully, with fewer deleterious side effects," said Gouaux.

Gouaux's latest dopamine transporter research is also important because it was done using the molecule from fruit flies, a dopamine transporter that is much more similar to those in humans than the bacteria models that previous studies had used.

The dopamine transporter article was one of two articles Gouaux had published in today's edition of *Nature*. The other article also dealt with a modified amino acid transporter that mimics the mammalian neurotransmitter transporter proteins targeted by antidepressants. It gives new insights into the pharmacology of four different classes of widely used antidepressants that act on certain transporter proteins, including transporters for dopamine, serotonin and noradrenaline. The second paper in part was validated by findings of the first paper—in how an antidepressant bound itself to a specific transporter.

"What we ended up finding with this research was complementary and mutually reinforcing with the other work—so that was really important," Gouaux said. "And it told us a great deal about how these transporters work and how they interact with the antidepressant molecules."

Gouaux's discoveries over the years in neurotransmission have established him as one of the top investigators in his field. His research has important implications for understanding the mechanisms of not just antidepressants, but also drugs used for the treatment of a wide range of psychiatric and neurological diseases.

Provided by Oregon Health & Science University