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# Neurotransmitter research may help promote better drug design for brain disorders

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Although drugs have been developed that inhibit the imbalance of neurotransmitters in the brain – a condition which causes many brain disorders and nervous system diseases – the exact understanding of the mechanism by which these drugs work has not yet been fully understood.

Now, researchers at the Hebrew University of Jerusalem, using baker's yeast as a model, have deciphered the mode by which the inhibitors affect the neurological transmission process and have even been able to manipulate it. Their work, reported in a recent article in the *Journal of Biological Chemistry,* raises hopes that these insights could eventually guide clinical scientists to develop new and more effective drugs for brain disorders associated with neurotransmitter imbalance.

All of the basic tasks of our existence are executed by the brain – whether it is breathing, heartbeat, memory building or physical movements – which depend on the highly regulated and efficient release of neurotransmitters – chemicals that act as messengers enabling extremely rapid connections between the neurons in the brain.

When even one part of the everyday "conversation" between neighboring neurons breaks down, the results can be devastating. Many brain disorders and nervous system diseases, including Huntington's disease, various motor dysfunctions and even Parkinson's disease, have been linked to problems with neurotransmitter transport.

The neurotransmitters are stored in the neuron in small, bubble-like

compartments, called vesicles, containing transport proteins that are responsible for the storage of the neurotransmitters into the vesicles.

The storage of certain neurotransmitters is controlled by what is called the vesicular monoamine transporter (VMAT), which is known to transport a variety of vital neurotransmitters, such as adrenaline, dopamine and serotonin. In addition, it can also transport the detrimental $MPP^+$, a neurotoxin involved in models of Parkinson's disease.

A number of studies demonstrated the significance of VMAT as a target for drug therapy in a variety of pathologic states, such as high blood pressure, hyperkinetic movement disorders and Tourette syndrome.

Many of the drugs that target VMAT act as inhibitors, including the classical VMAT2 inhibitor, tetrabenazine. Tetrabenazine has long been used for the treatment of motor dysfunctions associated with Huntington's disease and other movement disorders. However, the mechanism by which the drug affects the storage of neurotransmitters was not fully understood.

The Hebrew University study set out, therefore, to achieve an understanding of the basic biochemical mechanism underlying the VMAT reaction, with a view towards better controlling it through new drug designs.

The research was conducted by in the laboratory of Prof. Shimon Schuldiner of the Hebrew University's Department of Biological Chemistry; Dr.Yelena Ugolev, postdoctoral fellow in the laboratory; and research students Tali Segal, Dana Yaffe and Yael Gros.

To identify protein sequences responsible for tetrabenazine binding, the Hebrew University scientists harnessed the power of yeast genetics along with the method of directed evolution.

Expressing the human protein VMAT in baker's yeast cells confers them with the ability to grow in the presence of toxic substrates, such as neurotoxin $MPP^+$. Directed evolution mimics natural evolution in the laboratory and is a method used in protein engineering. By using rounds of random mutations targeted to the gene encoding the protein of interest, the proteins can be tuned to acquire new properties or to adapt to new functions or environment.

The study led to identification of important flexible domains (or regions) in the structure of the VMAT, responsible for producing optional rearrangements in tetrabenazine binding, and also enabling regulation of the velocity of the neurotransmitter transporter.

Utilizing these new, controllable adaptations could serve as a guide for clinical scientists to develop more efficient drugs for brain disorders associated with neurotransmitter imbalance, say the Hebrew University researchers.

**More information:** "Identification of Conformationally Sensitive Residues Essential for Inhibition of Vesicular Monoamine Transport by the Noncompetitive Inhibitor Tetrabenazine." Yelena Ugolev, Tali Segal, Dana Yaffe, Yael Gros and Shimon Schuldiner. November 8, 2013. *Journal of Biological Chemistry*, 288, 32160-32171. DOI: 10.1074/jbc.M113.502971

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