Organic cation transporters: Research into their structure facilitates targeted development of new drugs

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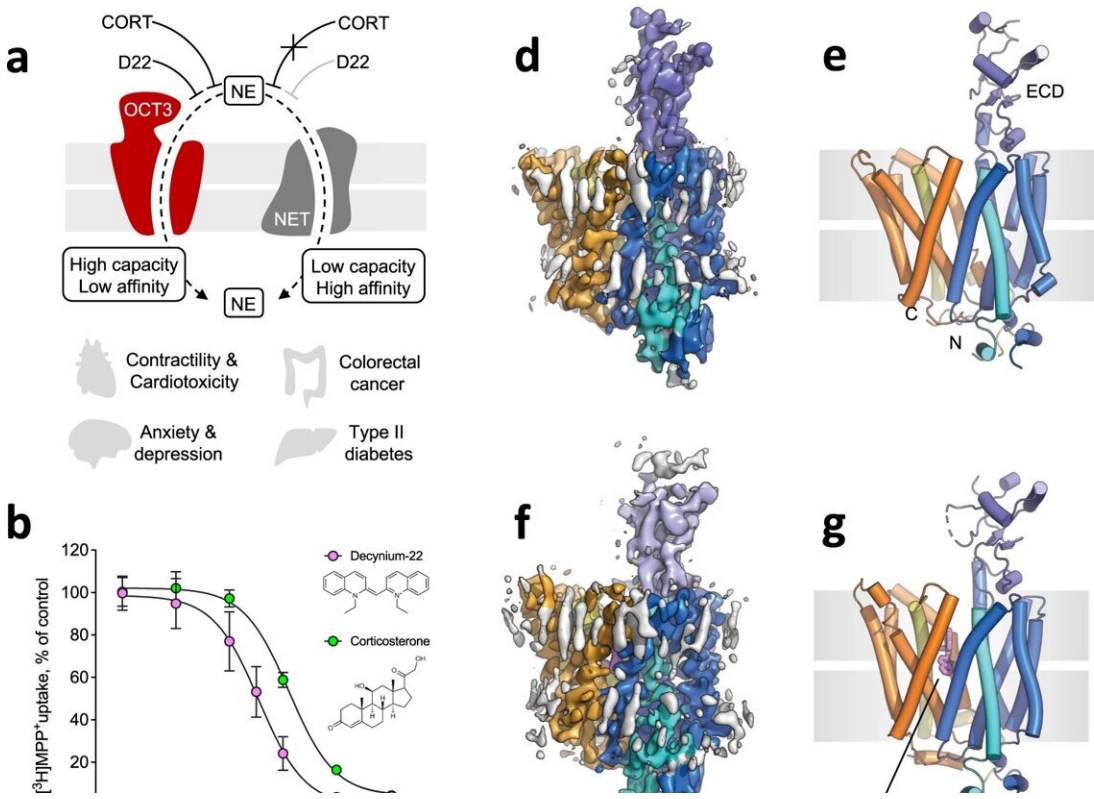

Structure and function of OCT3. **a** Schematic representation of OCT3; key features of the transporter are illustrated in the panel. **b** OCT3 transport inhibition by decynium-22 (D22) and corticosterone (CORT). The values correspond to mean ± SD; *n* = 3 represents three biologically independent experiments that are conducted with three technical repeats. **c** A scheme depicting the topology and the secondary structure elements of OCT3. **d**, **e** The

cryo-EM map (**d**) and model of OCT3 in nanodiscs at 3.2 Å resolution. The colors of the protein correspond to those in c; annular lipids are colored gray. **f**, **g** Same as **d**, **e**, for OCT3-D22 complex at 3.6 Å resolution (D22 colored violet). **h**, **i** Same as **f**, **g**, for OCT3-CORT complex at 3.7 Å resolution (CORT colored green). Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-34284-8

Monoamines are neurotransmitters in the central and peripheral nervous systems and they also transmit signals between cells and the brain. This transmission is followed by their reuptake into the cells by means of transporters. While the specific monoamine transporters have already been well studied, not enough is known about the organic cation transporters, which are high-capacity monoamine transporters.

A research team led by Julian Maier and supervised by Harald Sitte from MedUni Vienna's Center for Physiology and Pharmacology has now succeeded in mapping the structure of a hitherto little-studied cation transporter and has also investigated mutations found in neuropsychiatric patients. The study was published in *Nature Communications*.

Neurotransmitters are chemical messengers responsible for the transmission of information between neurons in the brain and the rest of the body. They influence our mental state, our sleep, pain processing and also muscles, blood vessels and hormone production.

These neurotransmitters are transported by means of special proteins located in the cell membrane. Once a neurotransmitter has been released from a cell in response to a stimulus and has acted on a receptor, it is reabsorbed into the cell by transporters. This efficient "recycling" saves the body from the need to constantly synthesize new neurotransmitters.

Neurotransmitters in balance

In monoamines, two main types of transporters perform this function. The specific monoamine transporters carry neurotransmitters, such as serotonin or dopamine, back into the cell after they have acted on the receptors. However, their transport capacity is low. Then there is the group of organic cation transporters (OCT), which perform a complementary function. The latter transport positively charged, i.e. cationic, neurotransmitters and have a high transport capacity.

Both groups work together and are important for maintaining the neurotransmitter balance in the body. Research carried out to date has focused on investigating the first group of specific monoamine transporters, for example in the medical application of serotonin reuptake inhibitors for treating depression. However, OCTs also have a major influence on the monoamine balance. They also influence pharmacokinetics and interact with medically administered drugs. They play a major role in the physical absorption and excretion of drugs.

On the trail of transporter variants

The research team led by physician Julian Maier and supervised by Harald Sitte from the Institute of Pharmacology at MedUni Vienna's Center for Physiology and Pharmacology specifically studied organic cation transporter 3 (OCT3). Working in collaboration with a Danish research group from the University of Copenhagen and the iPSYCH consortium, they were able to analyze genetic data from about 12,000 patients with neuropsychiatric disorders and compare them with those from a control group.

They looked to see which variants of transporters were detectable and how they were distributed. Maier then analyzed these variants in cell

systems in vitro and compared them with the so-called "wild type," the most prevalent normal form. It appeared that some transporters are apparently unable to transport any neurotransmitters at all, while others are able to transport even more than the "wild type."

Basis for targeted research

Working with the team of Volodymyr Korkhov at ETH Zurich, the researchers used cryo-electron microscopy, a high-resolution imaging technique, to obtain first-time insights into the structure of the OCT3 transporter and a specific characterization of its binding site. They were now able, aided by molecular dynamics-simulations performed in the group of Thomas Stockner from MedUni Vienna, to show how OCT3 functions, and which substances interact specifically with the transporter and why.

"Consequently, we are now in a better position to analyze the mutations found and explain, for example, why their transport capacity is greatly reduced or increased," says Julian Maier.

This would potentially lead to a variety of medical applications, such as the development of molecules that inhibit the reuptake of neurotransmitters by OCT3 in the central nervous system, and for cardiovascular indications. Study leader Harald Sitte explains: "Our results will facilitate targeted research into compounds that selectively interact with the transporter." The research team plans to conduct follow-up studies.

More information: Basavraj Khanppnavar et al, Structural basis of organic cation transporter-3 inhibition, *Nature Communications* (2022). DOI: 10.1038/s41467-022-34284-8

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