Researchers solve the mystery of the acid pump

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Researchers at Aarhus University, Denmark, have succeeded in identifying the mechanisms involved in what is known as the acid pump, which at the cellular level pumps acid into the stomach - in some cases leading to gastric ulcers and gastroesophageal reflux disease. The research results emanate from Jens Chr. Skou's sodium-potassium pump, for which he was awarded the Nobel Prize twenty years ago.

Smaller concentrations of gastric acid and thus fewer patients with gastric ulcers and gastroesophageal reflux disease. This is one of the perspectives contained in the research result, which postdoc Rikke Holm from the Department of Biomedicine recently has published in the prestigious scientific journal *Proceedings of the National Academy of Sciences (PNAS)*. The research took place as an international collaborative project between Professor Bente Vilsen's laboratory, Aarhus University, and the laboratory headed by Professor Pablo Artigas, Texas Tech University, Lubbock, Texas, USA.

The specific research result is basic research based on Nobel Prize winner Jens Chr. Skou's discovery of the sodium-potassium pump, which is a membrane pump that is necessary for the nerve cells to function.

"The sodium-potassium pump and the acid pump are very similar in many respects, and this is crucial for understanding the perspectives of the research results," says Professor Bente Vilsen.

Rikke Holm explains that the sodium-potassium pump creates an electrical current across the cell membrane. The current arises because the pump transports three sodium ions out of the cell for every two potassium ions that are pumped in. The acid pump does something similar, but this time with hydrogen instead of sodium ions - and with the crucial difference that the acid pump does not generate a current. It is electroneutral, unfortunately as we might say. Because if it were current generating - electrogenic - like the sodium-potassium pump, it would produce less acid in the stomach for the benefit of patients with gastric ulcers.

"We have shown that it is possible to remove the sodium-potassium pump's ability to generate current simply by replacing an amino acid in the sodium-potassium pump, cysteine, with another amino acid, which can be found in the acid pump, arginine. The replacement is accomplished by genetic manipulation, and the result is ground-breaking because it identifies arginine as the secret behind the acid pump's electroneutral function, which again determines the high acidic concentration in the stomach," says Rikke Holm.

Rikke Holm made her fundamental discovery during her PhD when she compared a number of different mutations of the sodium-potassium pump. The very unique properties of the arginine pump led her to contact an expert in electrophysiology, Dr. Pablo Artigas, who invited her to study in his laboratory. Working together, they performed the crucial electrophysiological studies on the mutated sodium-potassium pump, and the studies showed that the presence of the inserted positively charged arginine converts the sodium-potassium pump to an electroneutral pump just like the acid pump.

There is a long way to go before the research results can directly benefit patients, but the new knowledge about the acid pump and its mechanism - that it is possible to alter a pump's function - provides the basis for

continued work that may lead to reverse outcome: creation of electrogenic acid pumps. In the words of Bente Vilsen, the truth is that it is basic research that generates the knowledge forming the basis for the development of the vast majority of drugs and treatments.

Under pressure to name several possible future perspectives, Bente Vilsen mentions that the discovery of the electroneutral sodium-potassium pump also makes it possible to explore what an inability to produce current means for the development of the cells and the occurrence of diseases in e.g. the brain and kidneys, where the sodium-potassium pump plays a crucial role. But as Bente Vilsen says:

"Our discovery is as such basic research, and PNAS wished to publish it because we have shown the way to change one type of pump into another type of pump, which reaches into our innermost understanding of the membrane pumps. This may have some perspectives which we cannot necessarily fully assess and understand yet, and we should therefore not overstate these today."

More information: Rikke Holm et al. Arginine substitution of a cysteine in transmembrane helix M8 converts Na,K-ATPase to an electroneutral pump similar to H,K-ATPase, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1617951114

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