

PRESS RELEASE

Mystery About the Evolution of the Nervous System. Many Proteins Share the Same Functions.

A team from the Karl Landsteiner University in Krems, Austria, finds a high redundancy in proteins that modulate neuronal networks and neuronal signal transmission

Krems, Austria, 25. October 2022 – Not just three, but even five proteins share important roles in the formation and function of synapses and can substitute for each other. This discovery was made by a team of the research focus "Mental Health & Neuroscience" of the Karl Landsteiner University of Health Sciences Krems (KL Krems) and the CavX PhD program of the Medical University of Innsbruck. Most of these proteins are components of so-called calcium channels, and only recently the team had succeeded in discovering redundant functions for three of the proteins in synapse formation and neuronal signal transmission. The recent finding, that two additional proteins ($\alpha 2\delta$ -4 and Cachd1) can fulfill the same functions is surprising and raises questions about the evolution of the nervous system.

Ion channels serve to conduct signals in the nervous system, so it is essential that their function is tightly regulated. Proteins of the $\alpha 2\delta$ -family (pronounced "alpha-two-delta") play an important role in this process. They serve as regulatory subunits of calcium channels and hence for a long time they are known to regulate calcium currents. Recently, however, Univ. Prof. Dr. Gerald Obermair, head of the Division of Physiology at the KL Krems, and his team were able to show that three of the four $\alpha 2\delta$ -proteins are also chiefly involved in the formation of synapses and that they can substitute for each other in this fundamental function. This caused a considerable stir, as $\alpha 2\delta$ -proteins are associated with diseases such as epilepsy, autism, schizophrenia, and anxiety. Now Prof. Obermair and his research group have succeeded in showing that the last of the four proteins of this family and also another protein not only influence synapse formation, but also affect signal transmission.

Two is Better. Many are Best.

In contrast to the previously studied $\alpha 2\delta$ -proteins (isoforms -1, -2, -3), the now investigated $\alpha 2\delta$ -4 occurs predominantly in the retina of the eye but is hardly found in the brain. The current results, as Prof. Obermair explains, are even more surprising: "We were able to show in cell cultures that $\alpha 2\delta$ -4 can exert very similar functions in the brain as the previously studied proteins $\alpha 2\delta$ -1 to -3. Indeed, all these proteins can even replace each other in their most critical function. This seems wasteful and is remarkable in evolutionary terms."

On top of that, the team also studied a protein known as Cachd1. While this protein is structurally similar to the $\alpha 2\delta$ -proteins, it is still unclear whether it also serves as a subunit of ion channels. Unlike $\alpha 2\delta$ -4, however, it is abundantly found in the brain and has been linked to brain functions. This and its similarity to $\alpha 2\delta$ -proteins were reasons enough to take a closer look at the functions of Cachd1.

"And indeed," elaborates Cornelia Ablinger, first author of the study and a student in the CavX PhD program, "it turned out that Cachd1 can also take over the functions of $\alpha 2\delta$ -proteins. Hence, it can modulate synapse formation and also affect channel function." Further experiments with all $\alpha 2\delta$ isoforms and Cachd1 showed that the ability to substitute for each other does not come without subtle differences. For example, analyses of synaptic calcium signals identified minute differences indicating specific modulatory roles of each protein. A finding that allows Prof. Obermair to speculate on the apparent redundancy of the proteins: "It may well be that in the course of evolution they diversified one after the other to adapt the critical control of nerve signal transmission to the requirements of increasingly complex organisms."

Experimental Challenge

The surprising results were only made possible by ten years of preliminary work by Prof. Obermair's team. Actually, it was the ability of $\alpha 2\delta$ proteins to substitute for each other that posed an experimental challenge. Particularly, because first a cellular nerve cell model had to be developed in which all three genes for $\alpha 2\delta$ -1 to -3 were switched off. This endeavor turned out to be a big challenge, with a success rate of less than 5 percent.

However, once the team – which received a great deal of international attention – had overcome this hurdle, the questions could be experimentally tackled. The discovery that also $\alpha 2\delta$ -4 and Cachd1 can modulate synapse formation and differentiation was made possible by the preliminary work. Precise measurements of calcium signals of individual synapses provided evidence that $\alpha 2\delta$ -4 and Cachd1 can also modulate channel function. Following up on these questions, further cutting-edge research results can be expected at the research focus "Mental Health & Neuroscience" at the KL Krems.

Images available on request

Original publication: $\alpha 2\delta$ -4 and Cachd1 Proteins Are Regulators of Presynaptic Functions. C. Ablinger, C. Eibl, S. M. Geisler, M. Campiglio, G. J. Stephens, M. Missler & G. J. Obermair. *Int. J. Mol. Sci.* 2022, 23(17), 9885; <https://doi.org/10.3390/ijms23179885>

About Karl Landsteiner University of Health Sciences (2022)

At Karl Landsteiner University of Health Sciences (KL) in Krems, the comprehensive approach to health and disease is a fundamental objective for research and teaching. With its Europe-wide recognized bachelor-master system, KL is a flexible educational institution that is tailored to the needs of students, the requirements of the labor market as well as the scientific challenges. Currently KL hosts about 600 students in the fields of medicine and psychology. The three university hospitals in Krems, St. Poelten and Tulln ensure clinical teaching and research at the highest quality level. In research, KL focuses on interdisciplinary fields with high relevance to health policy - including medical technology, molecular oncology, mental health and neuroscience, as well as water quality and related health aspects. KL was founded in 2013 and accredited by the Austrian Agency for Quality Assurance and Accreditation (AQ Austria). www.kl.ac.at/en

Scientific Contact

Prof. Dr. Gerald Obermair
Dept. Pharmacology, Physiology &
Microbiology
Division Physiology
Karl Landsteiner University of Health
Sciences
Dr.-Karl-Dorrek-Straße 30
3500 Krems / Austria
T +43 2732 720 90 490
E gerald.obermair@kl.ac.at

Karl Landsteiner University of Health Sciences

Eva-Maria Gruber
Communications, PR & Marketing
Dr.-Karl-Dorrek-Straße 30
3500 Krems / Austria
T +43 2732 72090 231
M +43 664 5056211
E evamaria.gruber@kl.ac.at
W <http://www.kl.ac.at/>

Copy Editing & Distribution

PR&D – Public Relations for Research &
Education
Dr. Barbara Bauder
Kollersteig 68
3400 Klosterneuburg
M +43 664 1576 350
E bauder@prd.at
W <http://www.prd.at/>

