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Ultrafast Pace in the Brain: New Insights into Calcium Transport and Signal Processing

Researchers at the University of Freiburg, together with partners, have uncovered the mechanism of ultrafast transport by calcium pumps in nerve cells. These pumps, complexes of PMCA2 and neuroplastin proteins, operate at more than 5,000 cycles per second and terminate calcium signals within milliseconds – 100 times faster than previously known. They play a crucial role in rapid information processing in the brain. The findings open new perspectives for understanding neurological diseases and possible therapeutic approaches – targeting for example hereditary deafness. The studies have been published in Nature Communications and Nature.

Whether we think, hear, or move – all these processes are based on electrical signals in our nerve cells. They are triggered by the exquisitely precise interplay of ions such as calcium. But as important as calcium is for signal transmission: its amount must be kept at minimal level inside cells. An imbalanced calcium level may disturb cellular functions and, in the long run, promote diseases – including hereditary deafness. Therefore, rapid clearing of calcium by pumps is crucial and must occur after each signal. This task is carried out by complexes assembled from of a plasma membrane calcium adenosine triphosphatase (ATPase) subunit and a neuroplastin protein – so-called calcium pumps of the plasma membrane.

Cell physiological experiments led by Prof. Dr. Bernd Fakler, Director of the Institute of Physiology at the University of Freiburg and member of the Clusters of Excellence CIBSS – Centre for Integrative Biological Signalling Studies and BIOSS – Centre for Biological Signalling Studies, shows that these pumps operate at transport rates more than 100 times higher than previously assumed. By pumping calcium ions out of the cells at more than 5,000 cycles per second, the active, ATP-consuming calcium pumps of the cell membrane can lower intracellular calcium concentrations from 10 micromolar to less than 0.1 micromolar within just a few milliseconds.

“Our two studies show: pump complexes in the cell membrane remove calcium ions from nerve cells at transport rates of more than 5,000 cycles per second – 100 times faster than previously known. We also identified the key mechanism behind this fast pumping that is fundamental for millisecond information processing in our brain. Together, the results expand knowledge of signal processing in the brain and open new approaches for the development of drugs – for example against hereditary deafness”, says Prof. Dr. Bernd Fakler.

For comparison: calcium ATPases of intracellular membranes work at turnover rates of only a few tens of cycles per second. For their functional experiments, the team used calcium-activated potassium channels as ultrafast sensors, visualizing changes in the calcium concentration in the millisecond-range. Together with determination of pump complex densities in cell membranes by electron microscopy (about 55 complexes per square micrometer), the researchers were able to calculate the transport speed of the pumps. This calculation was carried out in collaboration with the group of Prof. Dr. Heiko Rieger at Saarland University. The results were published on August 20, 2025, in *Nature Communications*.

Membrane Lipid as Key Factor for Fast Transport

How are such high transport rates possible? The molecular principle behind this ultrafast operation was clarified by Freiburg physiologists, particularly Dr. Uwe Schulte of the Institute of Physiology, in collaboration with the Max Planck Institute of Molecular Physiology under the leadership of Prof. Dr. Stefan Raunser. This study will be published in *Nature*. The scientists conducted cryo-electron microscopy analyses at high spatial resolution (2.8–3.6 Å) of PMCA2-neuroplastin pumps in eight functional states of the transport-cycle. These studies show: calcium pumps interact with the membrane lipid PtdIns(4,5)P2. Its binding promotes key steps of the transport cycle, such as the rapid binding and release of calcium ions, thereby enabling the exceptionally high-speed pumping. Without this lipid interaction, transport slows down dramatically, as demonstrated by alterations of the pump structure by disease-causing mutations. Surprisingly, the researchers also discovered that the rapid pump activity of PMCA2-neuroplastin complexes is strongly inhibited by thapsigargin, a well-known inhibitor of intracellular calcium pumps – based on its perturbation of PtdIns(4,5)P2 binding to its site within the PMCA-subunit.

Importance for Brain and Medicine

Insights into the 3D structure of pump complexes and understanding of the lipid-dependent regulation of transport-activity could provide new drug targets for specific control of calcium-signaling pathways.

Publications:

Constantin C.E., Schmidt B., Schwarz Y. et al. (2025) Ca2+-pumping by PMCA-neuroplastin complexes operates in the kiloHertz-range. *Nature Communications*. doi:10.1038/s41467-025-62735-5

Vinayagam D., Sitsel O., Schulte U. et al. (2025) Molecular mechanism of ultrafast transport by plasma membrane Ca2+-ATPases. *Nature*. doi:10.1038/s41586-025-

Press release

21-Aug-2025
Source: Albert-Ludwigs-Universität Freiburg

Further information

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