09 | May 2014

MICE TIMES

Precise and punctual: the cellular postal service

Delivery problems can lead to diseases such as diabetes and Alzheimer's

Anyone who writes a letter and wants it to arrive at its destination should put in an envelope, write the address and the sender and stick a stamp on it. A similar principle applies in the microcosm of a cell, because here too letters and parcels are constantly being sent. Yet the cellular postal service does not operate with envelopes or cardboard boxes. The cargo to be shipped to another place within a cell or also outside it is transported in tiny blisters enclosed by a membrane that we call "vesicles". To ensure that this cargo is safely delivered, these vesicles also have to be furnished with corresponding address labels. But if something goes wrong with the delivery, diseases may occur, such as diabetes or Alzheimer's.

Randy Schekman, James Rothman and Thomas Südhof

The precious cargo, such as antibodies, hormones or neurotransmitters, should not only arrive at the right place, but also be delivered on time. In the dimensions of the cell, deviations on a scale of just a few nanometers or milliseconds can have fatal consequences. US American researchers Randy Schekman, James Rothman and the German-American Thomas Südhof have made a crucial contribution to the knowledge we have of the mechanisms and actors at play in cellular transport systems that were completely unknown about 30 years ago. For this brilliant scientific achievement they were awarded the Nobel Prize for Medicine last December.

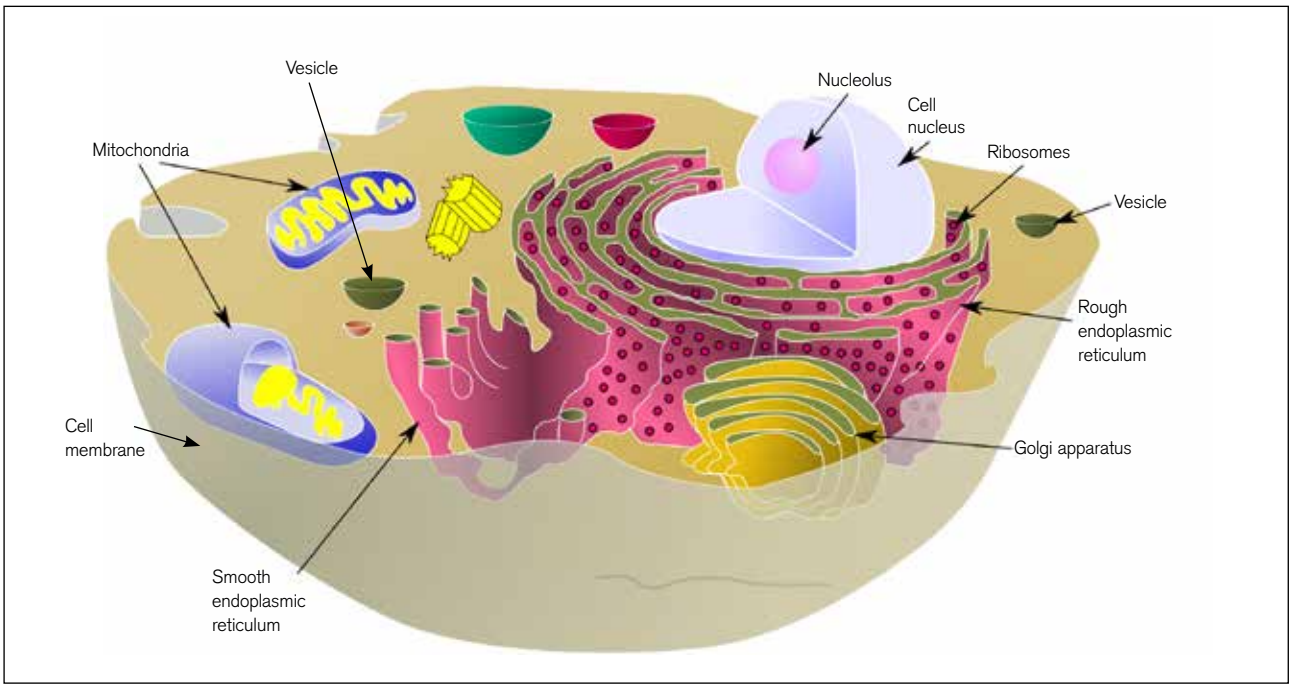


Fig. 1 Cell with its component parts
Source: http://www.zum.de/Faecher/Materialien/beck/11n/bs11-4n.htm

Fig. 2 Randy Schekman, James Rothman and Thomas Südhof all at http://www.badische-zeitung.de/panorama/medizin-nobelpreis-fuer-drei-zellforscher--75935525.html

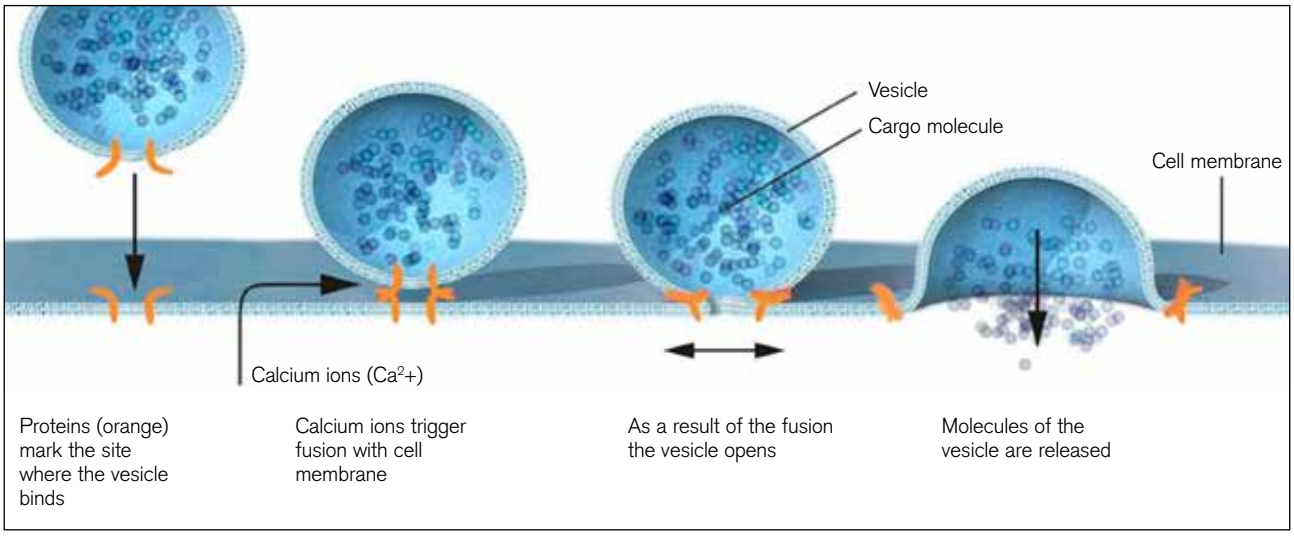
Basic principle of the transport system deciphered

Anne Spang from the Biozentrum of the University of Basel worked in the laboratory of one of the Nobel laureates, Randy Schekman, at the University of California during her postdoc until the end of the 1990s. The objective at that time, says biochemist Spang, was to establish which molecules were actually involved in the transport system. "In principle we only worked in test-tubes there, i.e. in vitro, and we purified membranes in order to simulate the mechanisms and try to understand how vesicles are formed and how they fuse with the target membrane", says Spang. In this way, they deciphered the basic principle of the transport mechanism. "If you want to study how vesicle transportation is regulated, you need whole cells. If you want to know how the whole works within the structure of the organ, you need animal models", says Spang.

Here the biochemist's team in Basel uses, for example, the nematode Caenorhabditis elegans. This worm offers a very good way of investigating how vesicle transportation works in the various organs, says Spang. Her team is looking in detail at the various transportation steps in the individual cells. Thus, for example, after they have been produced by the so-called endoplasmic reticulum (ER), proteins are transported to an organelle known as the Golgi apparatus and then distributed within the cell or carried outside the cell. All this takes place by means of vesicles that are passed on from one place to another. Vesicles filled with content are pinched off at the starting point, travel the necessary distance according to instructions and then fuse with the membrane of the target organelle. Here the cargo is released again. Now, vesicles are not disposable articles: they are used several times. "The process is rather like the use of milk bottles. These are emptied of milk and then returned to the producer, where they are refilled with milk", explains Anne Spang.

Quality control by the endoplasmic reticulum

Her team is occupied in particular with the pathways "back to the producer". Thanks to the return transportation, the valuable packaging material can be recycled. The freshly produced proteins repeatedly migrate in the vesicles, but also return again to the ER to undergo a kind of quality control. Here the cell checks to establish whether the three-dimensional structure of the protein to be transported is in order, says Spang. If it is not, the protein cannot fulfill its function properly. In the genetic disorder mucoviscidosis, for example, an important building block of a chloride channel, which actually belongs to the cell surface, is incorrectly folded and remains stuck in the ER. "An in-



Source: Tagesanzeiger 8 October 2013/Nobelpreiskomitee

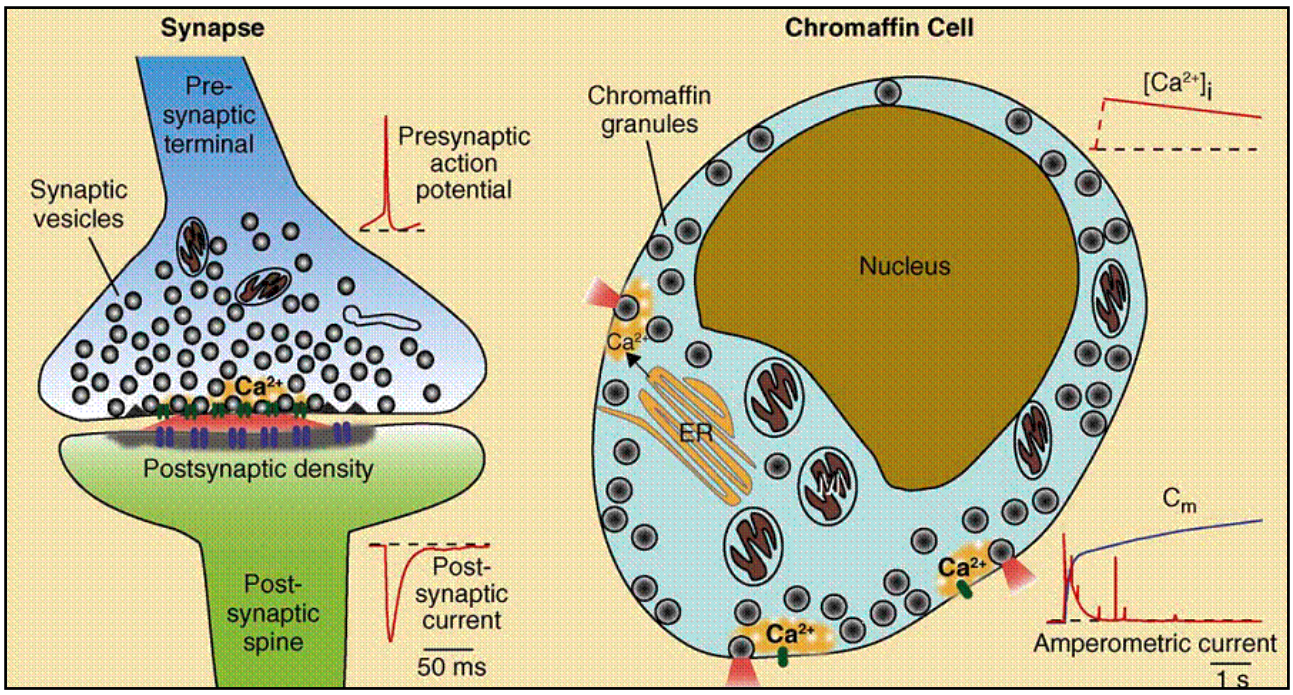


Fig. 4 left: The synapse is the basic structure of the neural network; in the presynaptic terminal are stocked vesicles that contain neurotransmitters, used to "pass" the signal from a neuron to another; when an action potential arrives to a presynaptic terminal, Ca2+ iones are released and helps vesicles to "mold" themselves with the presynaptic bouton and release the neurotransmitter docked inside them into the synaptic space; this mechanism actives the synapse and you can register a post-synaptic current, that means the passage of the signal.

right: Endocrine cell, where the vesicles containing hormon are docked in the whole cytoplasm of cell; whereas in the presynaptic terminal it had to be a action potential to originate the release the Ca2+ iones and then of vesicles, inside the endocrine cells there is a release of Ca2+, by stimulation or Ca2+-uncaging, that generate a slower current than in synapse; a slow release of hormon is a natural consequence of this pathway.

Source: www.sicencedirect.com, Cell biology of Ca2+ -triggered exocytosis, Zhipin P. Pang and Thomas C. Südhof

triguing question here is whether treatments can be developed that can abolish the misfolding, so that the important channel protein can be transported to its actual destination", says Spang.

Transport of information in neurons

A recycling of the transportation vesicles also occurs in another part of the body, namely at the nerve endings, i.e. the synapses. "The synapsis is the most important communication link between the neurons", says Jürgen Klingauf from the Institute of Medical Physics and Biophysics at the University of Münster. Klingauf is occupied with the so-called presynaptic membrane. This is the interlocutor, as it were, in the cooperation between the neurons transmitting information. When a neuron fires, it releases vesicles at the presynaptic membrane that are filled with messenger substances known as neurotransmitters. The production of the vesicle components actually occurs in the body of the cell, i.e. in the endoplasmic reticulum. Then the vesicles migrate to the branches of the nerves, where they fuse if necessary with the cell membrane and deliver the neurotransmitter to the synaptic cleft.

Recycling of vesicle components

The importance of the recycling of vesicle components becomes clear when one considers how long the neurons are, such as the neurons in the spinal column for example. The cell body – and thus the production site of the vesicles – lies at a distance of more than a meter from the nerve endings that can trigger a muscle contraction in the foot, for example. "Now, the synapse cannot wait hours for the vesicles to make this journey before they finally arrive at their destination", says Klingauf. And for this reason, he explains, there is a recycling mechanism directly on the presynaptic membrane that captures valuable vesicle proteins and recycles them.

The machinery is set up to work over long periods, explains the biophysicist.

"If small errors repeatedly occur here, it will have negative consequences, maybe not immediately, but

certainly in the long run." In this context, Klingauf mentions the protein alpha-synuclein, which also occurs in the presynapse and is probably involved in vesicle recycling. Current research work shows that it plays a crucial role in the pathogenesis of Parkinson's disease. But to study the function and also the malfunction of the processes involved here, simple models are no longer sufficient. "If we want to understand what is going on in the human brain, we have to do studies in the mammalian model", says Klingauf.

Processes must also be studied in animal models

Studies in cell cultures and animal models are also important for research into the causes of Alzheimer's disease. Lawrence Rajendran from the Center for Neurosciences at the University of Zürich is investigating whether Alzheimer's is due to a disturbance of the cellular transport pathways. All the molecular factors involved in the disease process are membrane proteins that are dispatched by the cell in vesicles. If the enzymes involved are active in the wrong part of the cell, this could trigger the accumulation of protein deposits, i.e. the amyloid plaques that are responsible for the death of the neurons. Experiments in mice have shown that the misdirected enzyme activity can be much better inhibited if a therapeutically active substance is selectively active in the vesicles of a cell because the researchers have furnished them beforehand with a corresponding address label.

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mice Times aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

Editors:

Basel Declaration Society, www.basel-declaration.org

Forschung für Leben

www.forschung-leben.ch I www.recherche-vie.ch

Author: Dr. Ulrike Gebhardt
Editorial staff: Astrid Kugler, Managing Director