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EDITORIAL

Nobel Prizes 2017 and their impact for physiology

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Physiology as the science that aims to understand and to explain body functions and their regulations from the whole body down to the single cell level has received rewards and input from the outstanding research that was awarded with the Nobel Prize 2017 in Physiology and Medicine and in Chemistry.

On Dec 10, 2017, Jeffrey Hall, Michael Rosbash und Michael Young received the Nobel Prize for Medicine and Physiology for their groundbreaking work on Chronobiology. Physiology teaches us that many physiological regulations and functions occur in diurnal cycles. The length of such cycles can be weeks such as the well-known estrous cycle or can last for 1 day reflecting the circadian rhythms. Many physiological regulations such as for example, blood pressure, body temperature, hormone secretion, and else show circadian cycles and some of them are further synchronized by the day light.

The roots for our today's understanding of the circadian rhythm reside in the early seventieth of the last century when the hypothesis came up that the circadian rhythm essentially involves gene transcription. Hall, Rosbash, and Young identified in the Drosopohila fly the *period*-gene as the core element of the circadian rhythm. They could further show that the gene product of the period-gene with assistance of the product of the *timeless*-gene migrates into the nucleus, where it inhibits transcription of the *period*-gene in the sense of a negative feedback. As a result, the cellular abundance of the *period*-protein oscillates. It does so with time interval of about 24 h in mammals thus leading to the circadian rhythm is not self-evident, because the cycle length of the period-protein oscillations depends on the abundance of the protein. The awardees could show that the protein *doubletime* delays the increase of period protein thus leading to the circadian rhythm.

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The review by Pilorz, Helfrich-Foerster, and Oster on "The role of the circadian clock system in physiology" in this issue of Pflügers Archiv takes up these molecular fundaments of circadian rhythms and gives an insight into our today's knowledge of circadian rhythms and how chronobiology has become a central part of physiology.

Also, on Dec 10, 2017, Jacques Dubochet, Joachim Frank und Richard Henderson received the Nobel Prize for Chemistry for their fundamental work for the development of the cryo-electronmicroscopy (cryo-EM). Not only physiologists are driven by the wish to have a picture from the topic they are working on. Since the mechanisms of transmembrane transport are a classical topic of physiology research, physiologists are particularly interested in the structure-function relationships of membrane transport and channel proteins. The smaller the structures of interest become, the more sophisticated methods for visualization are required. Electronmicroscopy which was developed in the 30s of the last century is commonly known as a method for the structural analysis of condensed material at the subnanometer resolution scale. Classic electron microscopy, however, does not allow studying structures and molecules in a hydrated environment, which is the normal biological condition. As an alternative approach, therefore, x-ray analysis of crystallized proteins had to be used to obtain structural information of proteins at the subnanometer scale, with all the difficulties and limitations associated with the crystallization of proteins. Cryo-electronmicroscopy now trespasses the limitations of the classic electronmicroscopy. The invention and combination of three maneuvers were required to develop cryo-EM from classic electronmicroscopy. First, the use of stabilizers that protect samples from destruction, second, the development of an algorithm for the 3D reconstruction from 2D pictures, and finally, an ultrarapid cooling of water solutions containing the structures of interest. With cryo-EM, the molecules of interest are not dehydrated and fixed but instead get shock-frosted. This procedure enables an easier and better visualization of proteins, DNA-protein, bacteria, and viruses as outlined by the Nobel Prize Committee. For physiologists, the structure-function relationships of membrane-inserted proteins

such as transporters or ion-channels are of particular interest, for understanding transmembrane transport and its regulation.

The review by Madej and Ziegler on "Dawning of a New Era in TRP channel Cryo-EM Structural Biology" in this issue of Pflüger Archiv summarizes the present state of cryo-electronmicroscopy and exemplifies the use of cryo-EM to get novel structure-based insight into the function of transient receptor potential (TRP) membrane channels.