



Warsaw, 22th of December 2022

Changes in ion concentrations responsible for seizures

An epileptic seizure may begin with firing of inhibitory neurons in the brain and changes in ion concentrations in the environment around the neurons. This mechanism, observed experimentally in an animal model of the guinea pig brain, was confirmed in a computer model of nerve cells, created at the Faculty of Physics of the University of Warsaw. The results of research conducted by a group of Polish and Italian scientists, published in the eLife journal, may contribute to the development of new antiepileptic therapies.

Epilepsy is one of the most common neurological diseases. Nearly 60 million people in the world suffer from it, including almost half a million Poles. Medications available on the market control seizures, but in some patients they do not work. For years, scientists have been trying to understand the mechanisms of this disorder in order to develop new, more effective methods of its treatment. A step towards the development of new anti-epileptic therapies may be the results of research by scientists from the Faculty of Physics of the University of Warsaw and Istituto Neurologico Carlo Besta in Milan, published in a journal eLife (<https://elifesciences.org/articles/68541v1>). A team of scientists has shown that seizures can start with the firing of inhibitory neurons in the brain and changes in ion concentrations in the environment around neurons. This mechanism, observed experimentally in an animal model of the guinea pig brain, was confirmed in a computer model of nerve cells, created at the Faculty of Physics of the University of Warsaw.

– If we open any book on neurology, we will find out that epilepsy is associated with an imbalance between excitation and inhibition in the brain. It is commonly assumed, that excessive activity of excitatory neurons induces a seizure, explains dr Piotr Suffczyński from the Faculty of Physics of the University of Warsaw, one of the authors of the publication in eLife. However, studies published in the last dozen or so years show that this is not always the case. – In 2008, a team of scientists from the Istituto Neurologico Carlo Besta in Milan observed a paradoxical increase in the firing of inhibitory neurons and a decrease in the activity of excitatory cells at the time of seizure onset - in an animal model of the guinea pig brain. Ten years later, it was possible to confirm the occurrence of this mechanism also in humans – explains the scientist.

Potassium accumulation hypothesis

For a long time, it was assumed that an epileptic seizure develops when successive neurons fire and excite each other through synaptic connections. Meanwhile, already in the 80s of the twentieth century, a publication appeared in "Nature" that showed that epileptic seizures do not require synaptic communication - you can block the communication between neurons and the seizure will continue. – In an experiment conducted in 2001, an epileptic seizure was induced in a brain slice in vitro. The two

halves of the slice were then separated by a scalpel incision. And although the physical connection between the two halves was broken - the synchronization between them was maintained, and the seizure continued. The researchers asked themselves: could something other than neurotransmitters be responsible for the development of a seizure? - says dr Piotr Suffczynski. In the next phase of the experiment, the movement of ions between the two halves was blocked by inserting a thin, impermeable membrane across the cut. As a result, the activities in the two separated parts become unsynchronized. "This confirmed that the induction and synchronization of epileptic seizures may not be caused by synaptic interactions but by ionic changes" the researcher explains.

Neurons are electrically charged cells, and the unequal distribution of positive and negative ions inside and outside the neuron creates the cell's resting membrane potential. The flow of ions across the membrane allows neurons to change their potential and generate short electrical impulses, or action potentials. – Sodium ions flow into the cell and potassium ions leave it. Sodium-potassium pumps work continuously to restore the original ionic balance by pumping potassium back in and sodium out of the cells. "However, when action potentials are fired at a high rate, sodium accumulates inside the cells and potassium accumulates in the space around the neurons. Elevated extracellular potassium increases the membrane potential of neurons, leading to their increased excitability, what in turn leads to further potassium accumulation. This is how an epileptic seizure is induced - explains dr Piotr Suffczyński. The "potassium accumulation hypothesis" was put forward as early as the 1970s. – At that time, it was rejected because scientists were unable to explain how the seizure ends. Today we know that, in addition to sodium-potassium pumps, there are glial cells in the brain, which not only nourish neurons, but also remove excess of potassium from the space around the neurons — explains the researcher.

The first complete seizure model

Based on experimental data, scientists from the Faculty of Physics of the University of Warsaw constructed a computer model simulating the mechanism of the course of an epileptic seizure. – Our biophysically realistic computational model consists of 5 cells: 1 inhibitory and 4 excitatory, glial cells and the extracellular space, in which the movement of ions takes place. Using this model, we were the first to show the potential mechanism of seizure initiation by inhibitory neurons through the initial accumulation of extracellular potassium." The model also shows how the mechanism that contributes to the cessation of seizures works. Sodium-potassium imbalance leads to increased activity of sodium-potassium pumps. – The pump moves two potassium ions into the cell and three sodium ions out of the cell in each pump cycle. This process removes one positive ion per cycle from the cell and leads to a decrease in the electrical potential of the cell. The increased rate of the pump causes a significant negative shift of the cell membrane potential and leads to seizure arrest, emphasizes dr Suffczyński. It is worth noting that the model developed by researchers from the Faculty of Physics of the University of Warsaw is the first complete model of a typical human epileptic seizure, characterized by a rapid onset of fast activity with low voltage, tonic phase, clonic phase, spontaneous termination and postictal suppression.

"Our results show that a seizure is a physiological process caused by the destabilization of potassium levels in the brain. This indicates the goals for new therapeutic strategies - adds the researcher from the Faculty of Physics of the University of Warsaw.

Faculty of Physics at the University of Warsaw.

Physics and astronomy at the University of Warsaw appeared in 1816 as part of the then Faculty of Philosophy. In 1825, the Astronomical Observatory was established. Currently, the Faculty of Physics at the University of Warsaw consists of the following institutes: Experimental Physics, Theoretical Physics, Geophysics,

the Department of Mathematical Methods in Physics and the Astronomical Observatory. The research covers almost all areas of modern physics, on scales from quantum to cosmological. The Faculty's research and teaching staff consists of over 200 academic teachers, 81 of whom are professors. About 1,000 students and over 170 doctoral students study at the Faculty of Physics at the University of Warsaw.

SCIENTIFIC PUBLICATION:

D. Gentiletti, M. de Curtis, V. Gnatkovsky, P. Suffczynski *Focal seizures are organized by feedback between neural activity and ion concentration changes*
<https://doi.org/10.7554/eLife.68541>

CONTACT:

Dr hab. Piotr Suffczyński
Faculty of Physics University of Warsaw
email: piotr.suffczynski@fuw.edu.pl
Phone: +48 55 32 868

RELATED WEBSITES WWW:

<https://www.fuw.edu.pl/faculty-of-physics-home.html>
Website of the Faculty of Physics University of Warsaw

<https://www.fuw.edu.pl/press-releases.html>
Press service of the Faculty of Physics at the University of Warsaw

GRAPHIC MATERIALS:

FUW221222b_fot01
https://www.fuw.edu.pl/tl_files/press/images/2022/FUW221220b_fot01.png
Biophysically realistic computational model consisting of 5 cells: 1 inhibitory and 4 excitatory, glial cells and the extracellular space, in which the movement of ions takes place. Visualization: Piotr Suffczyński, source: Faculty of Physics, University of Warsaw