New method to dampen nerve signals

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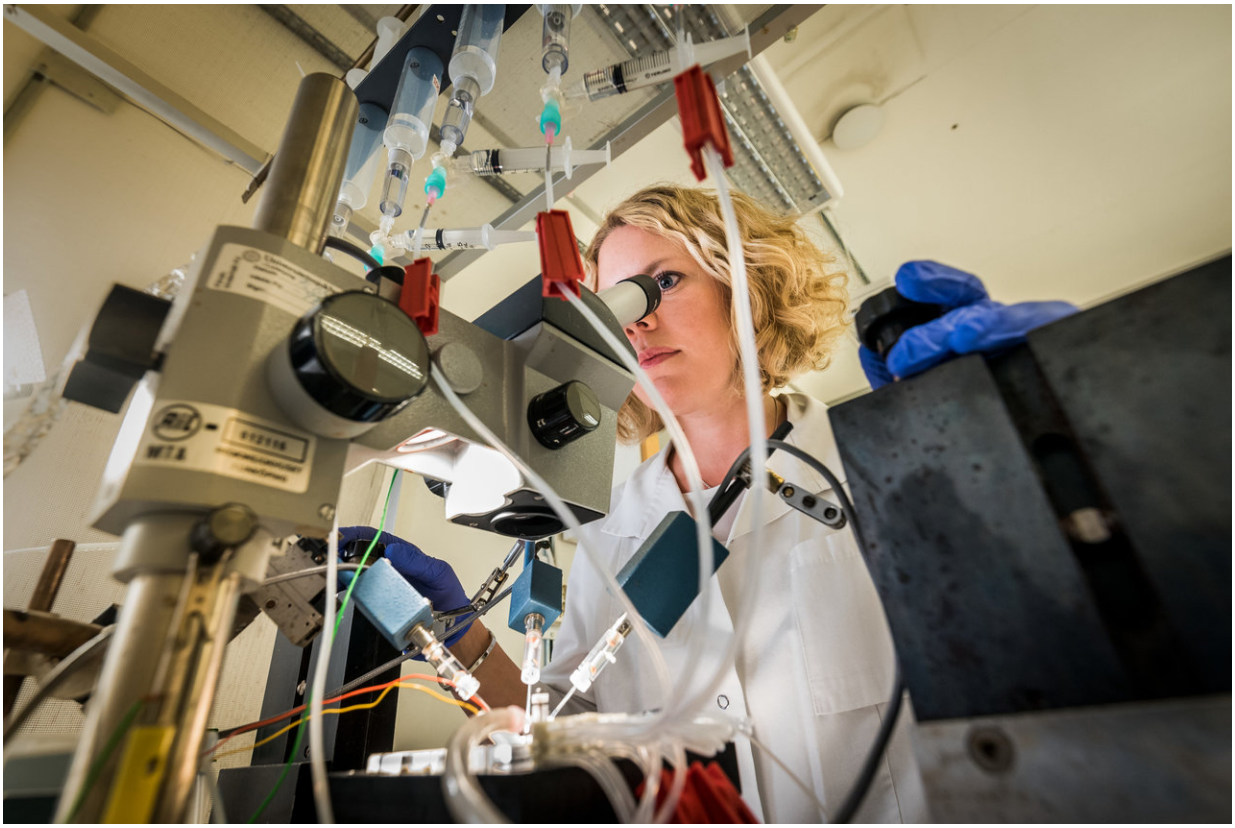

The researchers study the effects of substances on ion channels. Credit: Thor Balkhed/Linköping University

Researchers at Linköping University in Sweden have discovered a previously unknown molecular binding site that can influence electrical impulses in nerves. The results are presented in the journal *Science Advances*. The discovery opens the possibility of designing new types of

drugs against conditions such as epilepsy.

What do the toxins from arrow-poison frogs, puffer fish and scorpions have in common with drugs against epilepsy? The answer is that they all affect the ability of nerves to transmit electrical impulses by affecting the ion channels in nerves. Ion channels are small openings in the cell membrane of nerves that open and close like doors, in order to allow electrically charged ions to enter or exit. When enough ions have flowed into the nerve cell, an electrical impulse is released and transmitted along the nerve. Sometimes, however, it becomes far too easy for an electrical impulse to be released. Increased electrical excitability of nerves lies behind such conditions as epileptic seizures, disturbances in heart rhythm, and the experience of pain.

The anti-epileptic medication currently in use, and the animal toxins mentioned above, reduce electrical excitability by closing a certain type of ion channel. All such previously known molecules bind to locations at the ion channel itself. These binding sites are generally surrounded by water. In contrast, the cell membrane that the ion channel passes through is built from a bilayer of lipids, which are a form of fat that repels water-soluble substances.

"We show that a small molecule is embedded into the lipid bilayer and has direct contact with the ion channel. This is a fundamentally different type of binding site. One interesting question is whether we have naturally occurring molecules in the body that bind to ion channels in the same way. We probably do," says Fredrik Elinder, professor in the Department of Clinical and Experimental Medicine at Linköping University.

The researchers who have conducted the study have previously discovered that naturally occurring resin acids can regulate an ion channel that allows the passage of potassium ions. Resin acids are found

in the resin from conifers, such as the Swedish pine tree. Starting from one of the resin acids, chemists Xiongyu Wu and Peter Konradsson at the Department of Physics, Chemistry and Biology at LiU have created nearly 200 new molecules.

"All of the new molecules are based on the same basic skeleton, with very small differences between them. Some of them influence the voltage dependence of the ion channel, and we believe that it will be possible to exploit this mechanism in future drugs," says Nina Ottosson, principal research engineer in the Department of Clinical and Experimental Medicine, and leading author of the article.

The researchers have investigated the effect of the substances on a potassium ion channel from fruit flies. This ion channel is essentially the same in fruit flies and in humans. When the researchers wanted to examine in detail how the substances affect the ion channel, they discovered the new binding site. They have also identified a strong relationship between the chemical structure of the substances and their effect on the ion channel.

"Now that we have found this binding site, it's possible that we or other scientists can identify further molecules that bind to it. Our findings provide information about how we can modify substances to make them as effective as possible," says Fredrik Elinder.

Approximately one third of people with epilepsy still experience seizures even when receiving treatment, and currently available anti-epileptic drugs often have side effects such as tiredness and dizziness. The researchers hope that the drug-like substances can be developed into new drugs against epilepsy.

More information: Nina E. Ottosson et al. A drug pocket at the lipid bilayer–potassium channel interface, *Science Advances* (2017). DOI:

10.1126/sciadv.1701099