SYNERGIES: INTERDISCIPLINARY BAYER TEAM CONDUCTS RESEARCH INTO ION CHANNELS

Molecular gatekeepers

Whether a movement of the muscles or a beat of the heart: the cells in the bodies of humans and animals communicate with each other by means of electrical and chemical signals. The most important elements in the information cascade are ion channels. These protein molecules are therefore potential targets for new drug products, but also for insecticides in crop protection and parasiticides in veterinary medicine. Medical, veterinary and crop protection specialists at Bayer are now working together in interdisciplinary teams to find new active ingredients.

Ion channels are important **targets for human drug products**, but many antiparasitic agents and crop protection products likewise influence these cellular gateways to kill ticks, aphids and fleas.

Ion channels are important for **conducting stimuli** between nerve cells, for example. Excitation of a cell releases **signal molecules**.

These **signal molecules** bind to specific ion channels in neighboring cells, causing the channels to open.

Ions can pass through a channel at rates of up to **100 million ions per second**.

The **cell membrane** is impermeable to all **ions**. They can only pass through via ion channels.

Ion channels are specific: each channel only allows certain kinds of ion to pass.

The influx of ions produces an electrical **impulse** that the cell passes on.

The language of the cells

The human body comprises some 75 trillion cells, all of which have to cooperate so that life can function. The cells therefore communicate with each other. The basic principle involves excitation. Ion channels often play an important role in this process. They open and close as the result of chemical and electrical signals. When open, they form a gate through which electrically charged particles (ions) can pass into or out of the cell, thus regulating the electrical charge distribution in the membrane and conducting the originally received signal to other cells. This fundamental function makes ion channels an important target for many drug products, for example medicines to treat cardiac arrhythmia, hypertension and diabetes.

Everything has its place, especially in human, animal or plant biological cells. Only selected substances get inside the building blocks of life, thanks partly to ion channels. They control the cell membrane's entrances and exits and give only special electrically charged ions free access to the cell. And the ions have to hurry, because the channels close again after just a few milliseconds. Many cells have up to a million such gatekeepers, each of which is responsible for one specific kind of ion. This enables a targeted exchange of sodium, potassium, calcium and chloride ions in the nerves and tissues and makes possible the conduction of signals from one cell to the next. "Ion channels regulate the heart rhythm in humans and animals, for example, or convert stimuli like light, cold or heat into nerve signals," explains Dr. Thomas Müller from Bayer HealthCare's Global Drug Discovery department. Errors in this process can trigger severe disorders such as atrial fibrillation. Ion channels are therefore an extremely interesting topic in pharmaceutical research. "We're looking for new pharmacological targets in both cardiology and women's healthcare," says Müller.

Research collaborations: Dr. Thomas Müller, Dr. Dirk Heimbach and Dr. Horst Antonicek (left to right) are collaborating intensively in the development of new compounds for human, animal and plant health.

Scientists at Bayer CropScience are also conducting intensive research into ion channels, because the signal conduction process in crop pests such as aphids and spider mites or in parasites of companion animals likewise relies on the molecular gatekeepers. "There are many insects that can be harmful and are therefore unwanted in agriculture and animal health," says Dr. Ulrich Ebbinghaus-Kintscher, Head of Neurophysiology at Bayer CropScience. Ion channels have therefore long been a popular target for active ingredients such as imidacloprid, for example. This Bayer active substance combats sucking aphids and fleas on companion animals by binding to a specific ion channel, thus keeping the channel open. As a consequence, the insect's entire nervous system goes haywire. This mechanism of action helps imidacloprid not only protect apple orchards against sucking aphids but also dogs and cats against annoying fleas.

The patch clamp technique

The gold standard for studying ion channels is the patch clamp technique. This method involves sucking a membrane surface area or "patch" from a cell onto an ultra-thin glass pipette. This produces a tight seal between the cell and the pipette, which is filled with electrically conductive fluid. The current of a single ion channel can then be measured. The method was developed by Bert Sakmann and Erwin Neher, who received the Nobel Prize in Physiology or Medicine for this work in 1991.

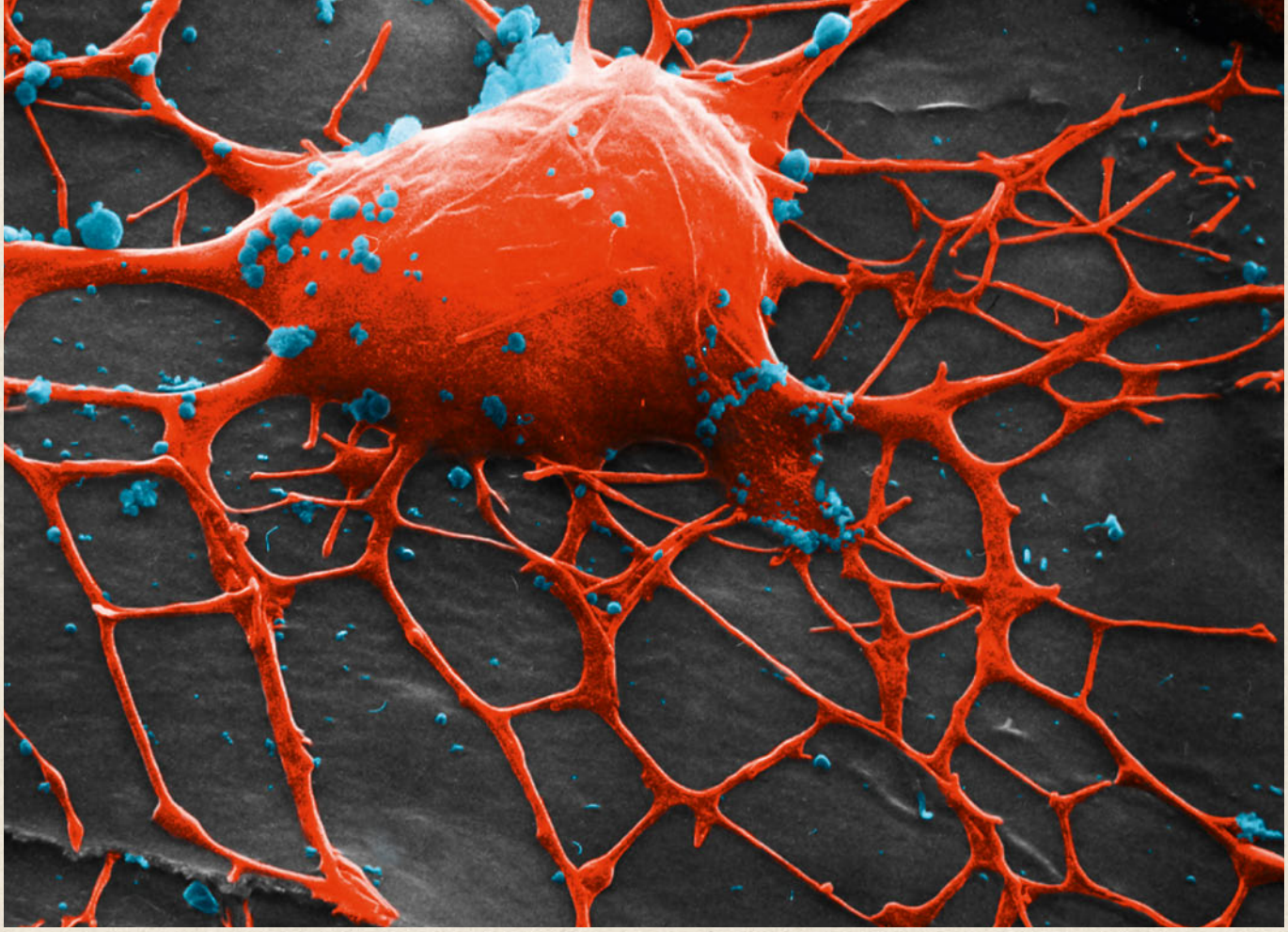
Today, scientists use this technique to develop substances that act on ion channels. It allows them to demonstrate in cell cultures whether the active ingredient influences the channel in the desired manner – in other words, opens, closes or blocks it.

However, in the early stages of drug development in particular, there are still numerous potential active ingredient candidates – too many to test them by hand. Scientists could only investigate about 100 compounds per month that way. Bayer has therefore invested in a state-of-the-art patch clamp robot, which is capable of testing some 20,000 active substances in cell cultures fully automatically every month.

Leveraging synergies: research in all areas overlaps during the early stages

Even though it may appear that there is a huge divide between applications in human medicine and those in veterinary medicine and crop protection, a look at the molecular details reveals numerous common features. "In the early stages in particular, there is a lot of overlap in the research in crop protection, veterinary medicine and human medicine," confirms Ebbinghaus-Kintscher. Bayer is focusing on these synergies: the company is networking its Life Science subgroups closely together as part of an initiative called the Nimbus project, and promoting the exchange of information with the objective of finding new approaches for new active ingredients.

Bayer scientists are also leveraging these synergies in the search for active substances that target ion channels. Their work is always focused on one specific ion channel: crop protection researchers like Ebbinghaus-Kintscher, for example, are concentrating their attention on an ion channel in aphids. Modulating this channel kills the insect pest. "First of all, we use cell cultures



Born communicators: nerve cells, or neurons, are perfectly adapted to passing on information, as their appearance clearly shows: each cell body has numerous structures branching off it that make contact to other neurons. The photo above shows a neuron under 3,000-fold magnification.

to test whether the new substances have the desired effect," explains Dr. Horst Antonicek, Head of Target Biology at Bayer CropScience. To this end, millions of molecules are tested by means of automated processes night and day. What's more, the crop protection scientists use not only their own substance libraries but also have access to the active ingredients from their colleagues at Bayer HealthCare. "Together, we can choose from more than 5 million compounds. This variety of chemicals increases the chance of actually finding a new lead structure," explains Antonicek.

Thanks to new technology, scientists can test more active ingredients in a shorter time

Frequently, however, thousands of molecules are still of interest after the first tests. "We then submit these compounds to electrophysiological testing using the patch clamp procedure," says Ebbinghaus-Kintscher. This method involves measuring the tiny electrical flow of ions through the channel using an extremely thin glass pipette, with and without an active substance. "They're complex tests. If we always did them manually, it would take years," says Antonicek. That's why there is now a state-of-the-art patch clamp robot at Bayer's Monheim site, which can manage 20,000 substances per month. "This is a quantum leap. Previously we could only test up to 100 substances in that time," says Antonicek.

Of course, not just Bayer CropScience benefits from this; all research departments can use the new ion channel platform. It also opens up new opportunities at Animal Health. "In the past, we were only able to take over established active substances from crop protection research," explains Dr. Dirk Heimbach, Head of Chemistry at the Animal Health department of Bayer HealthCare's Global Drug Discovery unit. "Now we have completely new opportunities for research into areas that are only of interest for animal health, such as tick- or worm-specific ion channels." And the results of these studies can, in turn, benefit the colleagues at Bayer CropScience.

But while there is extremely close cooperation at the start of the search for active substances, the scientists' roads diverge again once electrophysiological screening has been completed and the first prototypes have been selected. The jointly identified active ingredient classes are then tested with regard to their specific action on humans, animals and plants and then selectively optimized. Nonetheless, the initial stages of research into the molecular gatekeepers are very similar, and the joint efforts such as the screening platform enable better and faster development of new active ingredients, for human and veterinary medicine as well as for crop protection.

www.research.bayer.com/ion-channels
More information on this subject

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