

seizure

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Many years ago, I was sitting opposite a man whose body suddenly froze. His eyes seemed to be staring at something on the wall behind me while his left hand drew small circles in the air, repetitively. I had no idea what was happening to him until he came back to his senses and told me that he had just had an epileptic fit. Deeply embarrassed, he got up and left the room. Many of us will have witnessed a close relative, a friend, an acquaintance or perhaps simply a passerby, under the influence of an epileptic seizure – which are frequently more violent and alarming than the one I experienced that day. Epilepsy affects millions of people worldwide. However, what is happening on the molecular scale remains elusive. What we do know is that an epileptic fit is caused by neural activity that has suddenly gone out of control. In this light, researchers discovered two tarantula venom peptides – Aa1a and Ap1a – which inhibit channels that are used to relay signals in our central nervous system. Peptides such as these could perhaps be used to keep abnormal neural activity at bay in people suffering from epilepsy.



Komposition 1939

Otto Freundlich (1878-1943)

Until at least the 17th century, epileptic fits were thought to have a divine origin, or be caused by evil spirits. Even though, two thousand years earlier, the Greek physician Hippocrates had rejected the idea that epilepsy had anything to do with spirits but was a problem that stemmed directly from the brain and

could be medically treated. Nonetheless, for a very long time after his death, the only kind of healing offered was spiritual, and many suffering from epilepsy were shunned by society, if not interned. Still today, there are societies where epilepsy is believed to be associated with evil spirits, witchcraft or poisoning – and even sometimes considered contagious.

Defined as a disease of the brain, epilepsy seems to have a strong genetic predisposition although it can also occur in patients who have suffered brain trauma for example. When witnessing an epileptic fit, the first thing that comes to mind is that something has gone very wrong with the control of our body. In fact, we have no control over it anymore, as though the system for transmitting signals to and from our brain has suddenly gone haywire – which is exactly the case. Epilepsy is the result of a gross imbalance between neural activation and deactivation. Something our body is unable to cope with. So, it temporarily loses hold.

Neural activation and deactivation depend on the seamless coordination of the opening and closing of channels scattered throughout the central nervous system. The sum of concerted channel activation and deactivation allows us to remain in relative control of our mobility – but also of many other less tangible functions such as consciousness for instance. When channel concertation fails, there is an abnormal surge of neural excitation resulting in an epileptic seizure. A voltage-gated potassium

channel known as hEAG is important for human cognitive development. Scientists know this because mutated forms of hEAG give rise to syndromes known as Temple-Baraitser and Zimmermann-Laband, both of which result in mental retardation. Patients also happen to suffer from epilepsy – and this gave researchers the opportunity to understand the matter better.

With this in mind, animal venom is constituted of toxins, several of which specifically target channels involved in neural activation and deactivation. What better way to neutralize predators or prey than to meddle with their central nervous system by disrupting essential metabolic pathways that cause temporary paralysis – as the aggressor makes a run for it – or perhaps even death. For decades now, scientists have been singling out venom peptides that could have some kind of therapeutic potential. In the case of epilepsy, which is caused by the irrational and uncontrolled opening and closing of channels, a well-chosen toxin could perhaps counter this by guaranteeing some kind of regulation. So scientists scanned the venom of tarantulas, namely: *Avicularia aurantiaca* and *Avicularia purpurea*. The choice was far from innocent since the venom of both tarantulas is known to inhibit hEAG. Two peptides were extracted – kappa-theraphotoxin-Aa1a (Aa1a) from *A.aurantiaca*, and mu/kappa-theraphotoxin-Ap1a (Ap1a) from *A.purpurea* – both of which turned out to be potent hEAG inhibitors.

Aa1a and Ap1a are 81% identical, consisting of 36 residues with an amidated C-terminus and three disulfide bridges. Their singularity lies in the structure formed by the three bridges: a cystine knot. Imagine a loop formed by two of the bridges, and the third slides through it. This forms a cystine knot – in our case, an inhibitor cystine knot. Cystine knots are relatively common in venom toxins

because they confer chemical stability and resistance to enzymatic degradation, which means they can survive for a long time inside the victim. It is perhaps one of the rare times in life when the formation of a knot – whatever its nature – is not deemed a nuisance. Besides the cystine knot, there is another intriguing formation: a sort of ladder whose rungs are formed by the stacking of hydrophobic patches on one side of each inhibitor peptide. These molecular rungs may be necessary to form interactions with the target channel as well as the lipid membrane of brain cells. Certainly, molecular ladders such as these are frequently found in spider toxins whose role is to modify voltage-gated channels.

It is likely that Aa1a and Ap1a act by binding to the extracellular regions of hEAG where they cause a depolarising shift in the cell's membrane, reducing the probability that the channel opens by as much as 50%. In short, Aa1a and Ap1a do not deactivate the channels by blocking the central pore, for example, but inhibit them by exerting pressure, so to speak, on the pore domain. Of the two inhibitor peptides, Ap1a is the most potent inhibitor of hEAG, which makes it a potential candidate for the development of anti-epileptic drugs. Indeed, epilepsy affects as many as 70 million people worldwide – of all ages. Although seizures are always short-lived, there are invisible side-effects such as neurobiological and cognitive consequences but also psychological and sociological repercussions. Naturally, there are already many anti-epileptic drugs on the market. However, they are ineffective in as much as one third of persons suffering from recurrent bouts of epilepsy. The more scientists understand about the channels that are responsible for this widespread affliction, the better their knowledge will be to design drugs that will help everyone.

Cross-references to UniProt

Potassium voltage-gated channel subfamily H member 1, *Homo sapiens* (Human): O95259
Kappa-theraphotoxin-Aa1a, *Avicularia aurantiaca* (Yellow-banded pinktoe tarantula): A0A3F2YLP5
Mu/kappa-theraphotoxin-Ap1a, *Avicularia purpurea* (Ecuadorian purple pinktoe tarantula): PODQJ6

References

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