

throb

Vivienne Baillie Gerritsen

Many of us are acquainted with headaches. Brought on by lack of sleep, a lot of alcohol, too many tears, the time of month, or even the time of year, clammy weather, overbearing noise – you name it – headaches are a pretty common ailment many of us put up with on a regular basis. What is more, there are many painkillers on the market which are able to wipe away the symptoms within a matter of minutes. Migraines, however, are another piece of cake. The same environmental factors may trigger off a migraine but the symptoms are far more severe, frequently causing those suffering from one to remain bedridden until the pain has gone. Needless to say, headaches like migraines have no doubt been mankind's lot since our appearance on this planet, but what is responsible for the rhythmic thump inside our heads? There are two theories. One says that it all has to do with blood circulation. The second says that it's because of our neurons. Recently, scientists discovered a protein, known as TRESK, that seems to be directly involved in causing migraines. TRESK takes part in neuronal communication, thereby supporting the second theory.



Migraine Aura, by Pet Serrano

Courtesy of the artist

The term “migraine” is from the old French “migraine” derived from “hemicrania” – literally meaning “half a skull” – a term used by the Greeks to describe these debilitating headaches which typically affect one side of the brain. Over the centuries, suggested remedies could be as drastic as applying a hot iron to the head or inserting garlic into an incision made in

the temple. Some migraines – one third in all – give off tell-tale signals known as the aura, which warn those suffering from them of an oncoming attack. These signals are caused by neurological disturbances which are frequently visual – such as black spots, hallucinations or scintillating shapes – but can also be sensory such as limb weakness or a pins and needles sensation for instance.

Women suffer from migraine attacks more than men do. Why remains a mystery. Could it have something to do with their menstrual cycle? Possibly. Menopause certainly does seem to be one of the best ways to diminish migraine episodes. This said, there is no question that both genders are prone to the attacks. So what is it inside us which throbs? In the past years, researchers have managed to link a handful of genes to migraines but no one could point to one gene in particular. Until a few scientists discovered that a specific mutation in TRESK – for TWIK-related spinal cord potassium channel – could cause hereditary migraine with aura.

TRESK is one of the many types of potassium channel which has four transmembrane domains and two pore domains – themselves sandwiched between the first and second, and the third and fourth transmembrane domains. The importance of potassium channels was first recognised in the 1950s when researchers were developing the concept of electrophysiology and membrane

potential, and realised that potassium channels were at the heart of cell to cell communication. Indeed, as could be expected, potassium channels are found in every cell type of all forms of life and are known to be involved in a variety of physiological functions such as heart rate, muscle contraction and hormone secretion to name a few.

TRESK is found in the human spinal cord and brain. So, besides letting potassium ions through neuron membranes, what is the purpose of this particular channel in our central nervous system? It seems that TRESK has a direct role in the regulation of neuronal resting membrane potential as well as neuronal excitability – obviously of utmost importance when it comes to brain function. It has been suggested that the channel has a specific role in the pathway to pain and, conversely, in general anaesthesia. In the event of migraine with aura, a particular mutation in TRESK causes the channel to lose its function completely by truncating the second transmembrane domain in the channel. As a consequence, TRESK is unable to regulate neuronal excitability and – upon certain environmental cues such as bright lights, alcohol or tiredness – the first signs of neurogenic disturbance occur, soon followed by the characteristic debilitating painful pulses.

Since this particular mutated form of TRESK – and no doubt other mutations on the same protein, which remain to be discovered – has a direct role in causing migraines, an obvious therapeutic strategy would be to find a way to upregulate TRESK activity. Furthermore, the effects of TRESK inactivity could explain why patients who have to rely on immune-suppressants frequently suffer from migraine episodes. Indeed, immunosuppressive therapy involves calcineurin inhibitors which, in turn, inhibit TRESK function. There may be hope then for migraine sufferers who could benefit from such therapies either by using them as an immediate painkiller or as a prophylactic.

This could be great news for something which paralyses about 10% of the world's population. It has been estimated that migraine headaches are the most costly neurological disorder in the European Community – what with the medical costs involved and the consequent loss of professional productivity. However, finance and the work place aside, just a means to alleviate the throbbing pain which accompanies migraines is enough to look forward to and would offer a far more comfortable life to those who suffer from a chronic form of the condition.

Cross-references to UniProt

TWIK-related individual potassium channel, *Homo sapiens* (Human) : Q7Z418
Potassium channel subfamily K member 18, *Mus musculus* (Mouse) : Q6VV64

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