Scientists a step closer to understanding how anaesthetics work in the brain

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An important clue to how anaesthetics work on the human body has been provided by the discovery of a molecular feature common to both the human brain and the great pond snail nervous system, scientists say today. Researchers hope that the discovery of what makes a particular protein in the brain sensitive to anaesthetics could lead to the development of new anaesthetics with fewer side effects.

The study focuses on a particular protein found in neurons in the brain, known as a potassium channel, which stabilises and regulates the voltage across the membrane of the neuron. Communication between the millions of neurons in the brain – which is the basis of human consciousness and perception, including perception of pain - involves neurons sending nerve impulses to other neurons. In order for this to happen, the stabilising action of the potassium channel has to be overcome. Earlier studies on great pond snails by the same team identified that anaesthetics seemed to selectively enhance the regulating action of the potassium channel, preventing the neuron from firing at all – meaning the neuron was effectively anaesthetised.

The new research has identified a specific amino acid in the potassium channel which, when mutated, blocks anaesthetic activation. Lead author, Biophysics Professor Nick Franks from Imperial College London, explains how this will allow the importance of the potassium channel in anaesthetic action to be established:

"We've known for over 20 years now that these potassium channels in the human brain may be important anaesthetic targets. However, until now, we've had no direct way to test this idea. Because a single mutation can block the effects of anaesthetics on this potassium channel without affecting it in any other way, it could be introduced into mice to see if they also become insensitive to anaesthetics. If they do, then this establishes the channel as a key target."

The group carried out their new study, published in the 20 July issue of the *Journal of Biological Chemistry*, by cloning the potassium channel from a great pond snail and then making a series of chimeric channels – part snail and part human. The chimeras were used to identify the location of the precise amino acid to which the anaesthetic binds on the potassium channel, giving the team a clearer picture than ever before of the precise mechanism by which anaesthetics work.

This kind of research, explains Professor Franks, is important because understanding exactly how anaesthetics work may pave the way for the development of a new generation of anaesthetics which solely affect specific anaesthetic targets, which could potentially reduce the risks and side effects associated with current anaesthetics.

"At the moment, anaesthetics have many unwanted side-effects on the human body such as nausea and effects on the heart. This is because our current drugs are relatively non-selective and bind to several different targets in the body. A better understanding of how anaesthetics exert their desirable effects could lead to much more specific, targeted alternatives being developed, which could greatly reduce these problems," he said.

Source: Imperial College London