Ability of brain to protect itself from damage revealed

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The origin of an innate ability the brain has to protect itself from damage that occurs in stroke has been explained for the first time.

The Oxford University researchers hope that harnessing this inbuilt biological mechanism, identified in rats, could help in treating stroke and preventing other neurodegenerative diseases in the future.

'We have shown for the first time that the brain has mechanisms that it can use to protect itself and keep brain cells alive,' says Professor Alastair Buchan, Head of the Medical Sciences Division and Dean of the Medical School at Oxford University, who led the work.

The researchers report their findings in the journal *Nature Medicine* and were funded by the UK Medical Research Council and National Institute for Health Research.

Stroke is the third most common cause of death in the UK. Every year around 150,000 people in the UK have a stroke.

It occurs when the blood supply to part of the brain is cut off. When this happens, brain cells are deprived of the oxygen and nutrients they need to function properly, and they begin to die.

'Time is brain, and the clock has started immediately after the onset of a stroke. Cells will start to die somewhere from minutes to at most 1 or 2 hours after the stroke,' says Professor Buchan.

This explains why treatment for stroke is so dependent on speed. The faster someone can reach hospital, be scanned and have drugs administered to dissolve any blood clot and get the blood flow re-started, the less damage to brain cells there will be.

It has also motivated a so-far unsuccessful search for 'neuroprotectants': drugs that can buy time and help the brain cells, or neurons, cope with damage and recover afterwards.

The Oxford University research group have now identified the first example of the brain having its own built-in form of neuroprotection, so-called 'endogenous neuroprotection'.

They did this by going back to an observation first made over 85 years ago. It has been known since 1926 that neurons in one area of the hippocampus, the part of the brain that controls memory, are able to survive being starved of oxygen, while others in a different area of the hippocampus die. But what protected that one set of cells from damage had remained a puzzle until now.

'Previous studies have focused on understanding how cells die after being depleted of oxygen and glucose. We considered a more direct approach by investigating the endogenous mechanisms that have evolved to make these cells in the hippocampus resistant,' explains first author Dr Michalis Papadakis, Scientific Director of the Laboratory of Cerebral Ischaemia at Oxford University.

Working in rats, the researchers found that production of a specific protein called hamartin allowed the cells to survive being starved of oxygen and glucose, as would happen after a stroke.

They showed that the neurons die in the other part of the hippocampus because of a lack of the hamartin response.

The team was then able to show that stimulating production of hamartin offered greater protection for the neurons.

Professor Buchan says: 'This is causally related to cell survival. If we block hamartin, the neurons die when blood flow is stopped. If we put hamartin back, the cells survive once more.'

Finally, the researchers were able to identify the biological pathway through which hamartin acts to enable the nerve cells to cope with damage when starved of energy and oxygen.

The group points out that knowing the natural biological mechanism that leads to neuroprotection opens up the possibility of developing drugs that mimic hamartin's effect.

Professor Buchan says: 'There is a great deal of work ahead if this is to be translated into the clinic, but we now have a neuroprotective strategy for the first time. Our next steps will be to see if we can find small molecule drug candidates that mimic what hamartin does and keep brain cells alive.

'While we are focussing on stroke, neuroprotective drugs may also be of interest in other conditions that see early death of brain cells including Alzheimer's and motor neurone disease,' he suggests.

More information: 'TSC1 (hamartin) confers neuroprotection against ischemia by inducing autophagy' by Michalis Papadakis et al. *Nature Medicine*, 24 February 2013. DOI: 10.1038/nm.3097

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