Researchers discover a missing link in signals contributing to neurodegeneration

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In many neurodegenerative diseases the neurons of the brain are over-stimulated and this leads to their destruction. After many failed attempts and much scepticism this process was finally shown last year to be a possible basis for treatment in some patients with stroke. But very few targets for drugs to block this process are known.

In a new highly detailed study, researchers have discovered a previously missing link between over-stimulation and destruction of brain tissue, and shown that this might be a target for future drugs. This research, led by the A. I. Virtanen Institute at the University of Eastern Finland in collaboration with scientists from Lausanne University Hospital, University of Lausanne and the company Xigen Pharma AG, was published in the *Journal of Neuroscience*.

What is this missing link? We have known for years that over-stimulated neurons produce nitric oxide molecules. Although this can activate a signal for destruction of cells, the small amount of nitric oxide produced cannot alone explain the damage to the brain. The team now show that a protein called NOS1AP links the nitric oxide that is produced to the damage that results.. NOS1AP binds an initiator of cell destruction called MKK3 and also moves within the cell to the source of nitric oxide when cells are over-activated.. The location of these proteins in cells causes them to convert the over-stimulation signal into a cell destruction response. The team designed a chemical that prevents NOS1AP from binding the source of nitric oxide. This reduces the cell destruction response in cells of the brain and as a result it limits brain lesions in

rodents.

This translational research was funded mainly by the Academy of Finland, the European Union and the University of Eastern Finland and used the recently developed high-throughput imaging facilities at the A. I. Virtanen Institute. The researchers hope that continuation of their work could lead to improved treatments for diseases such as stroke, epilepsy and chronic conditions like Alzheimer's disease. As NOS1AP is associated with schizophrenia, diabetes and sudden cardiac death, future research in this area may assist the treatment of a wider range of diseases.

More information: Li, L. et al. Anita C. Truttmann, and Michael J. Courtney. The nNOS-p38MAPK Pathway Is Mediated by NOS1AP during Neuronal Death, *Journal of Neuroscience*, 8 May 2013, 33(19):8185-8201; doi:10.1523/JNEUROSCI.4578-12.2013. www.jneurosci.org/content/33/19/8185.abstract

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