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Researchers discover new ways to shut down signals involved in brain diseases

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A research team based at the University of Eastern Finland and the Turku Centre for Biotechnology have found new ways to block a pathway that may be responsible for several brain disorders, which could open the door to developing better treatments.

The protein NOS-1 generates nitric oxide, a chemical signal that is linked to neurological disorders from neurodegeneration, stroke and chronic pain sensitivity to anxiety and depressive disorders. These are now among the most common causes of disability and mortality, but decades of efforts have not led to a safe drug that controls NOS-1.

The researchers involved in the new work previously found that neurodegeneration or brain lesions caused by NOS-1 requires it to bind another protein called NOS1AP (or CAPON). They asked if damage can be reduced by preventing binding of NOS1AP to NOS-1, as NOS-1 cannot directly be controlled by drugs.

The researchers now reveal NOS1AP binds to NOS-1 in a surprisingly complex manner, and developed two separate ways to prevent it. By studying precisely how NOS1AP binds to NOS-1 they found two separate sites of interaction, by demonstrating that two different parts of NOS1AP are required for binding to

NOS-1 on separate sites. Each site could be blocked, one by a peptide previously developed by the team and the other by a new synthetic protein generated for this study. The second site was completely

unexpected as no similar interaction had been previously described and so nobody had known to look for it before. Blocking either site by itself reduced the damaging signals caused by NOS1 in brain cells. The results were replicated in several regions of brain tissue that are sensitive to degeneration caused by NOS-1. This means that it is now easier to design drugs that control damaging signals from NOS-1 in the brain because it can be done in two different ways or both ways may be combined. This might lead to development of new drugs for several different neurological diseases and conditions.

This research, published in the 13th May issue of the *Journal of Neuroscience*, was funded by the Academy of Finland, the European Union, the University of Eastern Finland, The Finnish Cultural Foundation North Savo Regional Fund, The Magnus Ehrnrooth Foundation and the University of Turku. The researchers hope that continuation of their work could lead to improved treatments for neurological conditions such as stroke and chronic pain as well as depressive and anxiety disorders. As NOS1AP and NOS-1 are associated with schizophrenia and sudden cardiac death, future research in this area may even assist the treatment of a wider range of diseases.

More information: "Unexpected Heterodivalent Recruitment of NOS1AP to nNOS Reveals Multiple Sites for Pharmacological Intervention in Neuronal Disease Models." *Journal of Neuroscience* May 13th 2015; 35(19):7349-7364. DOI: 10.1523/JNEUROSCI.0037-15.2015

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