Healthcare industry BW

A nasal spray for treating neurodegenerative diseases

Neuroscientists from Heidelberg have created the scientific foundations for a nasal spray that can stabilise the dendrites of nerve cells, thus reducing nerve damage and brain function losses following a stroke. Prof. Dr. Hilmar Bading and his team received the 2016 German BioRegions Innovation Prize for their invention and have set up a company called FundaMental Pharma to further accelerate the development of a marketable medicinal product.

Prof. Dr. Hilmar Bading, Managing Director of the Interdisciplinary Centre for Neurosciences and Director of the Institute of Neurobiology at the University of Heidelberg
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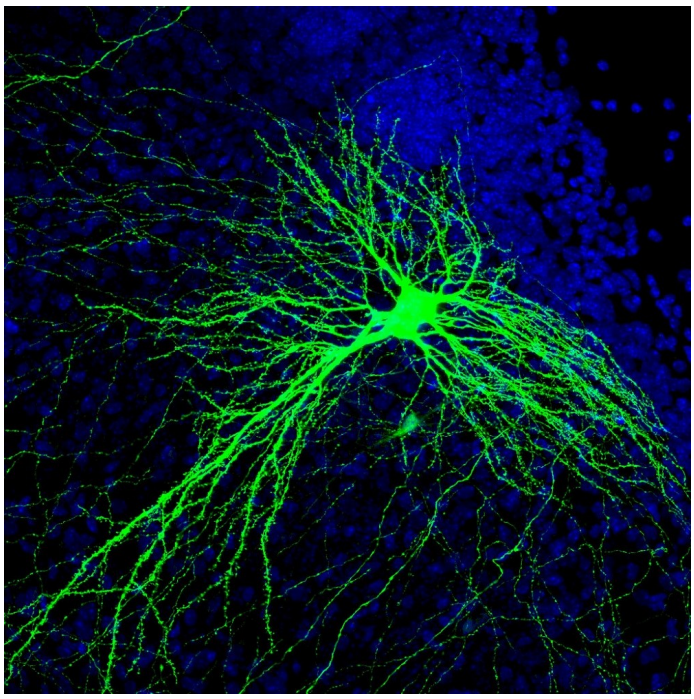
The nerve cells (neurons) of the brain have numerous tree-shaped branched projections called dendrites, with which they establish connections with other neurons. Various neurological diseases are characterised by dendritic trees that are shorter and simpler than those of healthy neurons. This may be associated with the loss of cognitive abilities. A group of researchers headed up by Hilmar Bading, a neurobiologist at the Interdisciplinary Centre for Neurosciences (IZN) at the University of Heidelberg, has identified a signalling protein called VEGFD ("vascular endothelial growth factor D") as a key regulator of neuronal arborisation. The protein is also a growth factor that stimulates angiogenesis, i.e. the growth of new blood and lymph vessels, thereby also promoting tumour growth and the metastatic spread of cancer cells. In the central nervous system, VEGFD is mainly involved in the maintenance of dendrite arborisation, basically acting as a "dendrite stabiliser".

Calcium as the key switch in the nucleus of neurons

Bading and his collaborators have shown that calcium can switch on signalling mechanisms in the

nucleus of neurons that control the survival of the nerve cells and cognitive abilities, such as long-term memory formation. The researchers were able to elucidate the complex signalling mechanisms switched on by nuclear calcium in cell cultures of hippocampus (a brain region that plays a key role in memory formation) neurons. The neurotransmitter glutamate, which is released as a result of a nerve impulse, activates so-called NMDA receptors at the neuronal synapses, which then serve as transmembrane calcium channels. Inside the nerve cell, calcium is bound to calmodulin and activates a gene expression programme (CREB/CBP transcription system) that leads to the transcription of genes that are key for long-term memory formation and neuron survival. One of these genes encodes VEGFD which controls maintenance of dendrite arborisation.

The researchers from Heidelberg have also shown that the nuclear calcium signal required for transcribing VEGFD and other genes induced by synaptic NMDA receptors is disrupted in patients with stroke or slowly progressing neurodegenerative diseases (such as Alzheimer's) by a second calcium signalling pathway that is induced by the activation of extrasynaptic NMDA receptors. This pathway leads to the shut-down of the CREB/CBP transcription system and the reduction of the expression of nuclear calcium target genes, in particular the dendrite stabiliser VEGFD. This results in the degeneration of dendrites, cell death and the loss of vital brain functions.



A "green fluorescent protein"-expressing neuron with numerous, highly ramified dendrites. Organotypical tissue culture derived from the hippocampus of a newborn mouse. © Daniela Mauceri, IZN

The researchers' work forms the scientific basis for a new way to treat neurodegenerative diseases. Bading and his collaborators, including junior professor Dr. Daniela Mauceri, have developed a drug based on VEGFD, a so-called VEGFD peptide mimetic whose application prevents the loss of dendrites, thus boosting the survival chances of neurons after a stroke, for example. The mimetic can easily be administered as a nasal spray.

From innovation to market: FundaMental Pharma GmbH

The use of VEGFD as an agent for stabilising dendrites is a radically new approach for the therapy of neurological diseases such as strokes that are associated with the loss of nerve cell structures. The researchers have also found that the therapeutic concept of using morphoceuticals, i.e. drugs that stabilise the structure of neurons, is suitable for treating other disease- and age-related degenerations that could either not be treated at all before or only insufficiently. These include dementia, amyotrophic lateral sclerosis, which is associated with the degeneration of motor neurons and paralysis, and glaucoma, which leads to the loss of nerve fibres.

The application of the drug in the form of a nasal spray has the great advantage that it is non-invasive and spares the patient undue discomfort, and can therefore be applied many times without any problems. The method is also highly efficient as the drugs directly enter the brain by way of the olfactory nerve in the nasal cavity, bypassing the blood-brain barrier. Prof. Dr. Christoph

Dr. Daniela Mauceri, junior professor and group leader at the Institute of Neurobiology at the University of Heidelberg
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Gleiter, a pharmacologist from Tübingen, has called this a “secret passage to the brain”. Thus, the peptide mimetic VEGFD can be administered intranasally to patients who have just suffered a stroke, thus maintaining and restoring the complex neuronal architecture of the dendrites that is key for the preservation of cognitive properties.

Hilmar Bading and his team were awarded the 2016 German BioRegions Innovation Prize for their innovative, application-oriented approach at a ceremony held during the German Biotech Days event that took place in Leipzig from 26th to 27th April. In order to further accelerate the development of the innovative drugs, the scientists have established FundaMental Pharma GmbH. Dr. Thomas Schulze, a business development manager from Munich, is also a member of the start-up team. The company founders hope that interested investors will provide financial resources for the further development of the new drugs so that patients can benefit as soon as possible.

Original publications

Oliveira AM, Bading H, Mauceri D: Dysfunction of neuronal calcium signaling in aging and disease. Cell Tissue Res. 357, 381-383 (2014)

Mauceri D, Freitag HE, Oliveira AMM, Bengtson CP, Bading H: Nuclear calcium-VEGFD signaling controls maintenance of dendrite arborization necessary for memory formation. Neuron 71, 117-130 (2011)

Article

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Further information

- Research group Bading - University of Heidelberg

The article is part of the following dossiers

Neurodegenerative diseases

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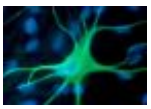

The neurosciences

Alzheimer's disease | neurodegenerative diseases | regenerative medicine | brain | synapsis | neuron | therapy | active pharmaceutical ingredient | stroke