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Novel perspectives for the Alzheimer´s disease therapy in a multitargeted approach

Alzheimer´s disease (AD) is the most wide-spread neurodegenerative disease and develops to a main problem for a society in which the people get older and older as a result of improved drug developments and therapies. The benefit of such drug developments becomes a burden for the society where the number of elder people is increasing consequently. Beside costs for the care of those people the fact that they suffer from a neurodegenerative decay caused by AD or related dementia diseases became a challenge for the pharmaceutical industry to develop novel drugs.

Early drug developments resulted in inhibitors of the acetylcholine esterase which shows enhanced activity rates in the brain of AD patients to reduce the necessary amounts of the neurotransmitter acetylcholine. Then just one drug followed that functions as antagonist of the neurotransmitter *N*-methyl D-aspartate which was also found deregulated in the brain of AD patients.

So all those early developments focussed on just one deregulated so-called target structure in the disease progression. The benefit for the patients was limited to the early states of the disease progression, but could not stop the disease progression.

One pathophysiological hallmark in AD was the deposit of amyloid plaques which could be found outside of the neuronal cells in the brains of AD patients. So following drug developments concentrated on the finding of effective target structures which are involved in the turn-over of the amyloid precursor protein to give the amyloid-β protein which consists of 42 amino acids and forms the amyloid plaques. Developed inhibitors and activators of involved enzymes as β-secretase and γ-secretase were not successful so far.

The most promising approach was the development of monoclonal antibodies directed against the insoluble amyloid plaques. The solanezumab antibody proved to remove those amyloid plaques from brain. A benefit for patients to improve the AD symptomatic in clinical trials could not be demonstrated in both the early and the later states of the disease progression.

How to proceed?
There is still one promising target structure for a perspective drug development: the tau protein. No-more functional tau protein can be found aggregated in deposits within the neuronal cells of AD patients as second pathophysiological hallmark in AD. Such aggregated tau protein is found hyperphosporylated at amino acid residues which are not found phosphorylated in normal brains. The hyperphosporylation is a result of an enhanced activity of various protein kinases which are found deregulated in the brain of AD patients. One early kinase which was identified to contribute to such a hyperphosphorylation was the glycogen synthase kinase (gsk) 3-β. Just one inhibitor of that kinase reached clinical trials, but disappointed similar to the previous AD drugs like the secretase inhibitors or the monoclonal antibody.

What may be the hope?
All those developments concentrated on just one target structure to follow a so-called monotargeted therapy. However, AD is known to be a multifactorial disease which means that many known factors

contribute to the disease progression. Various protein kinases have been discussed to make a contribution to the progression of AD. So protein kinases are promising target structures for a perspective multitargeting. We identified substituted small-molecule protein kinase inhibitors of the tricyclic benzofuropyridine type which showed partly nanomolar affinities to AD-relevant gsk-3β, extracellular-signal regulated kinase (ERK) 2 and C-Jun-*N*-terminal kinase (JNK) 3. Substituent-dependent effects on the respective kinase inhibitions are discussed and inhibitor binding modes to those kinases are presented based on enzyme docking studies. Inhibitor effects on the tau protein target structure are shown for first compounds in cellular studies to prove the enzyme conditioned effects.

Andreas Hilgeroth
Research Group of Drug Development,
Institute of Pharmacy, Martin Luther University Halle-Wittenberg,
Halle, Germany

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