"New Pathway in Treating Alzheimer's Disease-Moving Beyond Amyloid Strategy"

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ABSTRACT

Abbreviations: AD: Alzheimer's Disease; MAO B: Monoamine Oxidase B; MPTP: Mitochondrial Permeability Transition

Introduction

Despite extensive research, no new drugs for the treatment of Alzheimer's Disease (AD) have been introduced into therapy for over a decade. Nevertheless, the results of recent studies on the patho mechanism of Alzheimer's disease progression may raise some hopes as they identify and expose several major pathways of brain tissue homeostasis dysfunction, pathways that should undergo pharmacological correction to slow or inhibit the progression of neurodegeneration. While in the early stages of Alzheimer's disease, increased synthesis and oligomerization of β-amyloid and hyperphosphorylation of the tau protein play a key role in the patho mechanism of the disease, it is in the later stages of the disease that several known dysfunctions of the major homeostatic pathways in neurons, glial cells and cerebrovascular endothelium prevail in determining the progression of neuto degeneration, and the increasing accumulation of Aβ and P-tau deposits is a result of disease progression. The main driving forces of advanced neurodegeneration include:

a) Increased inflammatory reactions in neurons and glial cells, with the associated oxidative stress,

b) Deficiencies of neurotrophic growth factors and reduced regenerative capacity of neurons

c) Insulin resistance of the brain leading to disturbed metabolism of neurons

d) Reduction of the activity of the catenin Wnt-β pathway, which should properly integrate the above homeostatic mechanisms of brain tissue cells.

In order to more effectively inhibit the progression of neurodegeneration, it is necessary to use a combination therapy consisting of several drugs correcting the above dysfunctions or, alternatively, the use of multi-target drugs, i.e. when one drug restores several of these mechanisms. Recent studies have shown that many drugs used in clinical practice to treat various diseases can also inhibit the main mechanisms driving the progression of neurodegeneration. Majority of these drugs have been used in medicine for years, so their pharmacokinetics, toxicity and side effects, as well as their therapeutic dose range, are well understood. As a result, they can be relatively quickly introduced to the treatment of AD. It should be noted that a number of widely-used drugs from various pharmacological groups, "in addition" to the main therapeutic indications, also have a proven beneficial effect on neurodegeneration and may already be introduced into clinical practice in combination therapy of AD. There is a real hope that the

applied multi-drug therapy will effectively inhibit the progression of AD and turn it into a slowly progressing chronic disease.

Proposed Drug Combinations Should Include

a)   Drugs that reduce inflammation and oxidative stress in progressive AD (masatinib; rifampicine; glitazones: rosiglitazone, pioglitazone),

b)   Drugs that increase the sensitivity of neurons to insulin (insulin administered intranasally, IGF-1, GLP-1 and GIP; metformin together with glitazones)

c)   Drugs that improve the regenerative capacity of neurons (rasagiline; neurotropic growth factors: NGF, BDNF, GDNF – they do not cross the blood-brain barrier, should be administered in nanoformulations, intrathecally or intranasally; alternatively, small synthetic compounds administered orally with good brain penetration are currently in Phase II clinical trials as potent agonists of NGF receptors on neurons)

d)   Drugs that restore Wnt-β catenin signaling in coordinating the homeostatic responses of brain tissue cells (lithium chloride, sodium selenate, glitazones).

Examples of a Multifunctional Drug that Affects Several Different Factors / Mechanisms of AD Pathogenesis Include

a)   Rifampicin an antibiotic used to treat tuberculosis, legionellosis and leprosy in humans. Orally administered rifampicin (1 mg / day) to Tg2576 mice (Alzheimer's disease model) inhibited the formation of Aβ as well as the tau oligomer, decreased tau hyperphosphorylation, improved autophage-lysosomal function in neurons, decreased microglial activation in neuritis, and prevented synapse loss, and significantly improved memory in treated mice [1,2]. The pharmacokinetics, side effects, toxicity and drug interactions in humans are well understood. Rifampicin is a ready-to-use drug with great promise in the prevention and treatment of mild to moderate stages of AD.

b)   Rasagiline, a selective, irreversible Monoamine Oxidase B (MAO B) inhibitor used as an anti-Parkinson drug. In cultures of neuronal cells, the drug exerted a strong neuroprotective effect against various neurotoxins, cerebral ischemia, neurotrauma, and head injuries [3]. Its neuroprotective effect can be explained by the preservation of mitochondrial viability and the prevention of the opening of the Mitochondrial Permeability Transition (MPTP) pores, simultaneously with the activation of the anti-apoptotic protein Bcl2 and the downregulation of pro-apoptotic Bax proteins [3]. Rasagiline also exerts neurotrophic activity by stimulating alpha-secretase to produce Soluble, neurotrophic APP-α (sAPPα), which is supported by PKC and

MAP kinases. Rasagiline's neuroprotective, neurotrophic and anti-apoptotic effects are independent of MAO inhibition [3]. Rasagiline is currently in the second phase of clinical trials in patients with mild to moderate AD.

c)   Glitazones (thiazolidinediones): rosiglitazone, pioglitazone, troglitazone, are agonists of PPARγ (peroxisome proliferator-activated receptors) and activation of PPARγ reduces BACE1 transcription and activity [4,5]. Literature data indicate a beneficial effect of rosiglitazone and pioglitazone on the improvement of memory and learning abilities in murine AD models [5]. Additionally, it was found that in cultures of neuronal cells, the studied glitazones inhibited the key pathways of AD pathomechanism - rosiglitazone significantly decreased BACE1 transcription, thus decreased amyloidogenesis [5], and pioglitazone inhibited tau hyperphosphorylation and its oligomerization [6].

d)   Drugs that restore the activity of the Wnt pathway (lithium chloride, sodium selenate, rosiglitazone) may also have a multifunctional effect on the mechanisms of neurodegeneration. Restoration of Wnt signaling inhibits BACE1 expression, reduces Aβ production and aggregation, inhibits the activity of GSK3β kinase and reduces tau hyperphosphorylation [7], at the same time the Wnt system significantly improves cell regeneration and neuronal survival, increases the sensitivity of neurons to insulin, increasing the expression and activity of hexokinase and other glucose metabolism enzymes [8], and significantly reduces inflammatory reactions in the brain [9-14].

e)   Recently, the possible beneficial effects of modulating PPAR interactions with Wnt signaling in the treatment of AD have been highlighted. It should be noted here that in AD brains, Wnt-β catenin signaling is decreased, while PPAR-γ activity is increased, and the PPAR-γ and Wnt-β catenin pathways have the opposite effect, inhibiting each other. Surprisingly, however, in AD, administration of glitazone or non-glitazone PPAR-γ agonists revealed a number of beneficial effects: it significantly reduced learning and memory deficits, decreased Aβ microglia activation, and lowered inflammatory reactions in the brain, prevented the death of hippocampal and cortical neurons, and also stimulated/restored the activity of the Wnt-β catenin pathway which is significantly reduced in the Alzheimer's disease brain [15,16]. Therefore, despite initially elevated levels of PPAR-γ, compounds and drugs that are agonists of these nuclear receptors have been used in clinical trials to treat AD, improving some neuronal dysfunctions and, importantly, restoring the function of the Wnt-β-catenin pathway and enhancing its oversight over major mechanisms of neuronal homeostasis. Conversely, stimulation of the Wnt system activates PPAR gamma through the action of AMPK, Sirt 1 and PGC1-alpha [17].

This indicates that the Wnt and PPAR systems activate each other in AD neurons, and drugs that modulate the interaction of the two systems are currently considered as promising candidates for improved AD treatment. A growing number of extensive reviews indicate the possibility of slowing or even stopping the progress of Alzheimer's neurodegeneration with the use of combination multi-drug therapy [1,16-18]. The treatment strategies they propose often include attempts to reduce amyloid genesis and aggregation of Aβ and P-tau but focus mainly on correcting the main drivers of disease progression, i.e. increased inflammatory response, decreased availability of neurotrophic growth factors and decreased neuro regenerative capacity, the presence of features of insulin resistance, and other metabolic dysfunctions in neurons. The above-mentioned multi-target drugs have fulfilled these assumptions and extensive clinical trials should be started to verify their effectiveness. These are well-known drugs that have been used in medicine for many years to treat various diseases, and now their indications should be broadened in line with the newly described additional effects of AD. Combination therapy for Alzheimer's disease, used on a larger scale in clinical practice, will transform this debilitating disease into a very slowly progressing chronic disease. This is an important challenge for the near future.

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