ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2003, 63: 393-396

Therapeutic strategies for Alzheimer's disease based on new molecular mechanisms

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Abstract. Background and objective: Alzheimer's disease (AD) – the main cause of dementia – is characterized by the presence of neuritic plaques containing the amyloid-β peptide (Aβ) and an intraneuronal accumulation of tubule-associated protein called tau. The current and future therapeutic strategies for AD will be discussed. Currently available treatment used in AD is based on acetylcholinesterase inhibitors, since in the course of AD there is a substantial loss in cholinergic neurons. Another registered drug used in more severe AD is NMDA antagonist – memantine. Available strategies for AD include vitamin supplementation for reducing homocysteine levels, statins and non-steroidal anti-inflammatory drugs. The big hope of the last few years – vitamin E and estrogen supplementation have not been proved efficient, but more studies are needed. There are several strategies aimed at acting directly on Aβ or amyloid precursor protein (APP) processing: vaccination with Aβ peptide, Aβ passive immunization, beta and gamma secretases inhibitors. Nerve growth factors and neurotrophines could also be targeted by new therapies. Conclusions: a better understanding of the role of APP processing and folate and homocysteine in neuronal homeostasis throughout life consist revealing novel and relatively inexpensive approaches for preventing and treating AD.

Mini review

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Key words: Alzheimer's disease, treatment, acetylcholinesterase inhibitors, memantine, homocysteine, amyloid-β peptide

INTRODUCTION

Alzheimer's disease (AD) – the main cause of dementia – is characterized by the presence of neuritic plaques containing the amyloid-β peptide (Aβ) and an intraneuronal accumulation of tubule-associated protein called tau. Even though the amyloid hypothesis is not totally proved, biochemical and genetics studies implicated a central role for Aβ in the pathological cascade of events in AD (Selkoe 1999). In this review we focus on the possibility of developing novel anti-dementia strategies based on the latest molecular discoveries.

REVIEW OF THE PRESENT AND FUTURE THERAPEUTIC STRATEGIES

The traditional aim of AD treatment in clinical trials has been to improve cognitive abilities. Drugs for AD in our practical clinical work should be able to eliminate a triad of problems: cognitive decline, neuropsychiatric symptoms and functional deficits.

Currently available treatment used in AD is based on acetylcholinesterase inhibitors (AChE inhibitors), since in the course of AD there is a substantial loss in cholinergic neurons. AChE inhibitors are the primary treatment for the cognitive impairment and have a modest beneficial impact on the neuropsychiatric and functional outcomes for patients with AD (Trinh et al. 2003). In the clinical practice antipsychotic drugs or mood stabilizers are used to alleviate the neuropsychiatric symptoms in AD. Another registered drug for AD is memantine, which acts as N-methyl-D-aspartate (NMDA) antagonist and is used in more severe AD (Winblad and Poritis 1999).

An interesting approach is the vitamin supplementation. Among the widely used vitamins the most promising are vitamin B_{12}, vitamin B_6 and folic acid. They decrease the toxic aminoacid homocysteine. Furthermore, folate is a cofactor in one-carbon metabolism, during which it promotes the remethylation of

Table I

Current and proposed treatment approaches in Alzheimer's disease. *

Symptomatic	Causative	Preventive
Acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine)	Anti-amyloid strategies *vaccination *passive immunization *anti-amyloid agents such as gelsolin and ganglioside GM1 *beta and gamma secretase inhibitors	Anti-inflammatory drugs (NSIDs)
Antiglutamatergic (NMDA antagonists: memantine)	Interventions in tau hyperphosphorylation (glycogen synthase kinase-3β inhibition)	Antihypertensive strategies
	Nerve growth factor and other neurotrophins gene therapy	Anti-homocysteine therapy (Folic acid and vitamin B12 and B6)
		Estrogen replacement therapy
		Antilipid therapy (statins) (examples: atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)
		Antioxidants (vitamin E, Gingko Biloba)

* modified from Jelic and Winblad 2003

homocysteine – a cytotoxic sulfur-containing amino acid that can induce DNA strand breakage, oxidative stress and apoptosis. Recently elevation of homocysteine was found in AD patients and homocysteine seems to be an independent risk factor for developing the disease (Religa et al. 2003). The big hope of the last few years – antioxidants such as vitamin E and C, that were thought to prevent brain cell damage by destroying toxic free radicals – seems now to be unrelated to the AD risk according to the newest studies (Luchsinger et al. 2003); but in order to completely evaluate their usefulness longer observation is needed.

There are several strategies aimed at acting directly on Aβ as a causative agent for AD. The two proposed immunological ways consist of vaccination with Aβ peptide and Aβ passive immunization. A clinical trial of a vaccine made of synthetic Aβ 1-42 has been stopped in 2002, because patients developed encephalitis. The trials have been put on hold, but the concept is alive.

Well-characterized monoclonal antibodies against Aβ are needed to perform the trials using passive immunization. The new studies showed different proprieties of Aβ40 and Aβ42 in the way of forming the assembly (Bitan et al. 2003). Detailed characterization of the protofibril and fibril formations gives the possibility to test the other anti-amyloid agents preventing fibrillizations from the very early steps.

Another approach is to act on the amyloid precursor protein (APP) processing. There are three enzymes, which can be of interest: beta secretase, alpha secretase and gamma secretase. The simplest way would be to increase the alpha cleavage or to decrease the beta and gamma secretases activities. Beta secretase is a single enzyme whereas gamma secretase is a complex of several different proteins, such as presenilin, pen-2, aph-1 and nicastrine. Research on gamma secretase inhibitors led to a discovery of new substrates for this enzyme and brought out the question about safety of the complete blocking of gamma secretase in humans.

Nerve growth factors and neurotrophines could also be targeted by new therapies. Growth factor gene therapy, when patient's fibroblasts transfected with NFG are transplanted to the brain, is currently in a clinical trial (Tuszynski 2002). This approach will lead to a possible cure of severe AD as compared to all the previously described methods, that mostly prevent or slow the pathological processes down and do not help in the late stage of the disease.

NEW APPLICATIONS OF REGISTERED DRUGS

There are several drugs on the market that have a potential to be used for the treatment or/and prevention of AD. Epidemiological findings show that non-steroidal anti-inflammatory drugs (NSAIDs) are able to decrease inflammation in the brain and decrease more amyloidogenic forms Aβ42 (Weggen et al. 2001). Multi-center analysis indicated a decreased prevalence of AD in patients taking statins (reviewed by Crisby et al. 2002). Prospective studies in the clinically relevant dosages have shown that statins influence brain cholesterol metabolism, however, without influencing Aβ secretion (Fassbender et al. 2002). Therefore it is thought that statins lower the inflammation in the brain, but more research is needed for a decisive answer. The effect of statins as antilipidic drugs, is also beneficial, as AD patients have hypercholesterolemia and disturbed lipid metabolism (Czyzewski et al. 2001).

On the other hand, currently, the estrogen supplementation in woman seems to be less promising than expected. Even if we do not mention the side effects of this treatment, the biological plausibility of the estrogen hypothesis in dementia is its strongest plea, whereas studies in humans are far from conclusive.

CONCLUSION

A better understanding of the role of APP processing and folate and homocysteine in neuronal homeostasis throughout life consist revealing novel and relatively inexpensive approaches for preventing and treating AD and others neurological disorders.

ACKNOWLEDGEMENTS

We would like to thank SADF, Dementia Foundation, Gamla Tjänarrinor and Svenska Institutet for their support.

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Received 12 March 2003, accepted 2 April 2003