

Strategies, Molecular Targets and Animal Models Useful for Developing Therapies for Alzheimer's Disease

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In this Special Issue of Current Medicinal Chemistry-CNS the reviews cover mechanisms and biological models relevant to Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD), review neurodegenerative mechanisms leading to cognitive impairment and dementia, propose novel pharmacological approaches for defined "drugable" molecular targets, suggest relatively unknown but useful animal models for testing neuroprotection, and lastly examine the role of oxidative stress in AD and the possibility of developing strategies aiming at reducing it.

The first review "Diagnosis and Treatment of Alzheimer's Disease" by M. Monczor is a comprehensive description of the field of AD, highlighting the following difficulties:

Challenge	Unmet Needs
Diagnosis	Better and objective diagnostic tools
Following disease progression	Better prognostic tools for evaluating MCI –to-AD evolution
Evaluating treatment outcomes	Tools to evaluate drug efficacy early and objectively –especially during clinical trials–
Prevention	Education / lifestyle changes
Treatment	Effective drugs and perhaps new approaches

The cholinergic basal forebrain neurons which innervate the cerebral cortex and hippocampus play a key role in cognition and memory [1]. These neurons first atrophy, and it is thought that after atrophy the neurons degenerate and are lost. It has been suggested that initial atrophy results in MCI and the consequent degeneration in AD.

In the present review Monczor establishes that one of the more difficult challenges in developing new treatments for MCI/AD is that we are largely limited by assessment of cognitive status and there are no objective measurements of disease state or disease progression. Thus, evaluation of drug efficacy is difficult especially when the placebo effect has been estimated at detectable in ~30% of patients in clinical trials [2,3].

Recent progress in imaging techniques and the development of ligands for measuring reduced blood flow and metabolism, increased glial activity, and high A β amyloid deposits as markers of disease [4-6] should offer some solutions. However, these markers are surrogate markers not always well-correlated with severity of disease and their prognostic value is yet to be determined. I would suggest that imaging neuronal atrophy or neuronal loss may be the best direct biomarker. Alternatively imaging biomarkers directly implicated in neuronal loss may also be useful.

There has been a long-standing discussion concerning therapeutic strategies for AD. Whether to develop therapies aiming at reducing symptoms (i.e. cholinesterase inhibitors), at reducing neuronal loss by targeting elements involved in neuronal death (i.e. antioxidants, caspase inhibitors, anti-inflammatories, anti-A β), or reducing neuronal loss by neuroprotection (i.e. neurotrophic growth factors) is still debated.

The second review "Strategies to diminish the A β load in Alzheimer's Disease" by A.C. Cuello and K.F.S. Bell focuses on strategies aimed at reducing A β levels. The relevance of this therapeutic target, is supported by the well documented mechanisms linking the A β protein to the AD pathology. The trends of the A β causality in AD are well based on genetic, molecular biological and neuropathological evidence. While other causalities of AD are being entertained and argued, the A β target remains a widely investigated target in the AD pathogenesis in both academia and pharmaceutical industry.

The review of Cuello and Bell summarizes some of the main strategies aimed at preventing and or reversing A β aggregation in the CNS and highlights the advantages and disadvantages of each of these current approaches.

Regarding neuroprotection, the survival and phenotypic maintenance of cholinergic basal forebrain neurons are dependent on endogenous Nerve Growth Factor (NGF) acting through NGF receptors normally expressed in the soma and terminals of

these cells [7-9]. In the mature CNS, cholinergic basal forebrain neurons (CBF) which innervate the cerebral cortex and hippocampus play a key role in cognition and memory [1]. In ageing and cognitive disorders such as AD, CBF neurons first undergo atrophy and eventually degenerate [10,11]. This process correlates with progressive reduced NGF receptor density, specifically the TrkA receptor [12-14]. Indeed, reduced density of TrkA (but not of the common neurotrophin receptor p75) is a reliable biomarker of progressive deteriorating cognitive ability [15]. These studies show an almost linear correlation between loss of TrkA density and the severity of disease. Thus, targeting TrkA receptors with imaging ligands may be desirable as a diagnostic/prognostic biomarker, and perhaps even as a therapeutic target particularly for MCI.

Exogenous administration of NGF as a ligand of TrkA and p75 receptors has been used as an experimental therapeutic agent in aging and stroke animal models, and in human AD patients [16]. Exogenous NGF reversed the age-dependent changes in CBF neurons, and improved performance in spatial memory tasks. The effect of NGF was long-lived and persisted after discontinuation of delivery [17]. However, NGF therapy for AD patients failed because of CNS delivery problems, toxicity, pleiotropic effects and other side-effects (back pain, weight loss) [18-21].

Given the fact that experimental therapy with neurotrophin poypeptides failed, the question is whether neurotrophin receptors expressed in cholinergic neurons are drugable. The third review “Neurotrophin small molecule mimetics: candidate therapeutic agents for neurological disorders” by F. Longo *et al.* suggests that small molecule agonists can be developed.

Recently, in an aged model of cognitive impairment we demonstrated that a small molecule TrkA agonist ligand is efficacious and can delay behavioral deficits, can enhance the cholinergic phenotype, and can revert cholinergic atrophy to a degree comparable to NGF but without side effects [22]. While age-related cognitive impairment and AD are not the same disease, these data validate the neurotrophic approach. Ongoing experiments using transgenic mice AD models will reveal whether or not neurotrophic protection holds for AD in these animal models.

Moreover, as suggested above, it may be possible to label TrkA small molecule ligands with isotopes amenable for Positron Emitting Tomography (PET) or other relatively non-invasive methods, so that they can be used to monitor TrkA density repeatedly over time in patients. Because TrkA density correlates with disease state, such ligands would allow an objective evaluation of treatment outcome and to monitor drug efficacy early and objectively at a relatively low cost. These are all important and often limiting issues during clinical trials.

The fourth review “Glaucoma: validated and facile *in vivo* experimental models of a chronic neurodegenerative disease for drug development” by M. Rudzinski *et al.* focuses on open angle glaucoma as an animal model of neurodegeneration. The glaucoma model is underutilized, although it has several advantages. Notably, glaucoma and AD have several mechanisms in common.

	AD	Open Angle Glaucoma
Known Agents	A β , -secretases/presenilins, tauopathies, ApoE4, impaired NGF processing or utilization	High intraocular pressure
Phenotype	Cholinergic atrophy/death	Retinal ganglion cell death (optic nerve dysfunction)
Disease State	Memory/cognitive deficit leading to dementia	Loss of peripheral vision leading to total vision loss
Shared features	slow, chronic and cumulative neurodegenerative disorders	
	Selectively affect a subset of neurons	
	Caspase-mediated apoptosis	
	Compromised retrograde/anterograde neuronal transport	
	Excitotoxicity has been implicated	
	Neurotrophins seem to be protective to some degree	
	Deleterious immune/inflammatory mediators	

Both diseases are slow, chronic and cumulative neurodegenerative disorders; both selectively affect a subset of neurons; in both caspase-mediated apoptosis is involved; in both the inflammatory responses are deleterious; in both the retrograde and anterograde neuronal transport are compromised, in both excitotoxicity has been implicated, and in both neurotrophins seem to be protective to some degree. Rudzinski *et al.* suggest that the exploration of a glaucoma animal model may be desirable to screen neuroprotective compounds rapidly *in vivo*.

The last review “Alzheimer’s Disease and oxidative stress: the old problem remains unsolved” by Moreira *et al.* is a comprehensive description of the role of oxidative stress in AD. Perry and colleagues discuss evidence that oxidative stress is intimately associated with Alzheimer’s disease. Vascular atrophy, together with imbalances of glucose metabolism and severe

energy impairment contribute in the early pathophysiology of AD. Lipid peroxidation is a marker of neuronal damage and apoptosis; and oxidation of various proteins, RNA and DNA are found in the brains of AD patients.

A rationale has evolved for the use of various compounds with direct or indirect antioxidant properties. Some mixtures (e.g. Ginko Biloba) have gained acceptance through epidemiological or retrospective studies and evidence based prospective studies are still evolving.

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