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Review Article

Review of Intraventricular Infusion Approaches to the Treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease is the most common neurodegenerative disorder. Currently available therapies have limited symptomatic efficacy and do not alter disease progression. Immunotherapeutic approaches using anti-Aβ antibodies injected systemically have shown some reduction in amyloid plaques but are associated with a number of side effects. Intraventricular delivery methods for direct intracerebral delivery of antibodies against amyloid plaques are being developed with significant therapeutic potential without the complications seen with systemic infusions.

Keywords: Alzheimer's disease, Immunotherapy, Intraventricular infusion

Introduction

Alzheimer's Disease is the most common neurodegenerative disorder. The number of people who are developing this disabling disorder continues to increase. The current treatments have limited efficacy. The two principle events involved in the pathophysiology of Alzheimer's disease include the misfolding, aggregation and brain deposition of amyloid-β (Aβ) peptide in amyloid plaques along with the deposition of misfolded tau protein in neurofibrillary tangles [1]. Development of effective therapeutic treatment strategies is urgently needed. One approach which has been investigated is to use antibodies against Aβ which can disrupt the build-up of amyloid plaques [2]. However enthusiasm for the use of systemic antibodies against Aβ has been diminished due to adverse effects including meningoencephalitis and leukoencephalopathy [3-5]. It should be noted that while intravenously administered or systemic passive immunization against Aβ holds promise as a disease-modifying therapy for Alzheimer's disease, the blood brain barrier prevents the majority (~99%) of the anti-Aβ antibody from reaching its intended brain target. This results in the requirement for considerably higher doses, and greater systemic exposure of a therapeutic antibody. Furthermore in a phase II trial using anti-Aβ humanized monoclonal antibody (Bapineuzumab), removal of amyloid plaques was confirmed as detected by positron emission tomography (PET), but no cognitive improvement was documented [6]. It should be noted however in a more recent study using a mouse model, memory deficits were rescued following passive immunization of mice using an antibody against Aβ [7]. In another recent study, intracerebroventricular infusion of an inhibitor of the β-secretase enzyme significantly reversed the behavioral deficit and reduced brain Aβ levels in a transgenic mouse model of Alzheimer's disease [8].

Alternative approaches using immunotherapy techniques for treatment of Alzheimer's disease are being pursued.

Intraventricular Infusion Approaches

Several agents have been infused into the ventricular system of Alzheimer's Disease patients in an attempt provide a meaningful treatment. A variety of different agents have been used for intraventricular infusion. Bethanechol chloride, a muscarinic agonist that decreases synthesis of acetylcholine, has been administered into the ventricular system is patients with Alzheimer's disease with minimal therapeutic benefit [9-12]. Nerve growth factor which is known to rescue compromised cholinergic neurons and reverse memory impairments [13,14] has also been infused into the ventricles of patients with

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Alzheimer's disease [15,16] although limited clinical efficacy was observed. Another strategy has been to infuse gangliosides, an abundant neuronal plasma membrane component, into the ventricles of patients with Alzheimer's disease although any therapeutic value of this treatment strategy was difficult to determine [17,18].

Passive injection of antibodies against Aβ into the ventricular system for treatment of Alzheimer's disease has been developed in animal models. In normal mice, intraventricular injection of Aβ has been shown to rapidly perfuse the entire brain within 24 hours [19]. In a transgenic mouse model of Alzheimer's disease, intraventricular injection of Aβ was found to significantly reduce plaque formation without any evidence of perivascular hemorrhage or inflammation [20,21]. Furthermore the dose of antibody required was 10- 50- fold lower than those used with systemic delivery of the same antibody [21]. In addition systemic delivery of the same antibody resulted in aggravated vascular pathology, while this was not found following intraventricular infusion of the antibody [21].

The challenges of intraventicular infusion cannot necessary be extrapolated from mouse models to humans, given that the mouse brain is much smaller than a human brain and there may be differences regarding the blood brain barrier. To address this issue, an important extension of the mouse findings has been carried out in non-human primates using a humanized anti-Aβ IgG antibody [22]. Unlike in mice, intraventricular injection of antibodies do not easily perfuse into the primate brain. Antibodies however can be distributed within the primate brain following long-term infusion. Using aged Stumptail Macaque monkeys that have significant accumulation of amyloid pathology comprised of dense core along with diffuse-type plaques particularly in temporal cortical regions, a three month intraventricular infusion of humanized anti Aβ antibody resulted in a significant reduction of Aβ-42 positive parenchymal plaques in the cerebral cortex [22]. Furthermore infusion of the antibody did not alter the frequency or severity of amyloid accumulation in the brain vasculature. Although the animals displayed no abnormal clinical signs during the infusion period, there were changes noted in the ventricular geometry and intracranial pressure.

Conclusions

The widespread and significant reduction of amyloid-β following the three month intraventricular infusion of low dose of humanized anti-Aβ antibody in non-human primates clearly demonstrates that targeted intracerebral passive anti-amyloid immunotherapy offers a promising therapeutic approach for the management of amyloid pathology in Alzheimer's disease. Furthermore the intraventricular infusion strategy should avoid the complications observed with intravenous infusion of antibodies against Aβ which include dermatitis, pulmonary edema, allergic/anaphylactic reactions, acute renal failure, venous thrombosis and aseptic meningitis [23,24].

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