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Review

Alzheimer's disease and Down's syndrome: Treating two paths to dementia ☆

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ABSTRACT

Successful therapy of dementia, like any disease, depends upon understanding its pathogenesis. This review contrasts the dominant pathways to dementia which differ in Alzheimer's disease (AD) and in Down's syndrome (DS). Impaired clearance of neurotoxic amyloid beta peptides (Abeta) leads to dementia in AD. In DS over-production of Abeta plays the dominant role in the development of dementia. It follows, therefore, that the therapy of AD and DS should reflect a different balance between the dominant agent that inhibits the synthesis of Abeta in the brain in AD and increase the clearance of Abeta from the cerebrospinal DS.

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1. Introduction

Thomas Kuhn, in his book The Structure of Scientific Revolutions (1962), proposes that the path to scientific progress is made up of a succession of major steps that he terms "paradigm shifts" resulting in the evolution of thinking. In the field of dementia a major step has been the concept of the amyloid cascade described by Hardy and Selkoe [1]. According to this hypothesis dementia can result from an imbalance between the greater production and reduced clearance of Abeta in the central nervous system (CNS). The next paradigm shift was to individualize treatment of different forms of dementia based on the primary defect in Abeta pathophysiology. As will be discussed below, impaired clearance of Abeta from the CNS is dominant in Alzheimer's disease (AD). In contrast, in DS over-production of Abeta within the CNS is dominant.

The modern history of dementia began one hundred years ago when Alois Alzheimer described extracellular amyloid plaques in the brain of a woman with dementia [2]. Her illness now bears his name. The cerebral amyloid plaques that Alzheimer recognized are now known to be made up of fibrils of Abeta produced by secretase-mediated cleavage of the amyloid precursor protein (APP). When Alzheimer identified the cellular pathology of AD, human life expectancy in the USA was only 50 years, so that AD, which occurs in approximately 1% of 65 year old persons, was a rare disease. A century later, with life expectancy surpassing 75 years in most economically developed countries, AD has become a frequent and highly feared illness among the rapidly expanding population of elderly people.

In contrast, the frequency of DS at birth has remained fairly stable at approximately 1 in 700 live births. However, the number of individuals with DS who develop dementia has greatly increased as

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medical care of younger adults and middle aged persons allows prolonged survival late into adulthood.

2. Late-onset, sporadic, AD is associated with impaired clearance of Abeta from the central nervous system

The cerebral amyloid plaques that Alzheimer saw under his microscope had the staining properties of carbohydrates. For this reason, the cerebral plaques were initially described as "amyloid" or "starch like". The insolubility of the amyloid fibrils that made up these cerebral plaques prevented their true chemical composition from being recognized until 1984 when Glenner and Wong reported that the amyloid fibrils in the cerebral plaques in AD were composed of Abeta peptides [3]. The following year, Masters et al. not only confirmed that the cerebral plaques in AD were comprised of Abeta but also showed that cerebral plaques in demented adults with DS were also made of Abeta [4]. In contrast to sporadic AD, persons with DS are at an increased risk of early onset dementia, which usually occurs before 60 years of age in individuals who exhibit the childhood mental retardation and characteristic facial features first described by Down [5]. Thus, despite similar cytopathology in the two diseases, DS can be recognized very early in life before dementia is evident whereas in AD there are no obvious risk factors predicting dementia to come. This is important as it offers hope that defining early markers of dementia risk in DS might permit treatment that could delay or prevent the onset of dementia in DS.

This would not be the first time that an understanding of the pathogenesis of a rare, early-onset genetic disease could lead to a successful therapy of a more common disease that normally occurs later in life. Recall the studies of Brown and Goldstein on another early-onset genetic disease, familial hypercholesterolemia. Their studies revealed the pathogenesis of this rare disorder and led to the discovery of the statin drugs that revolutionized the treatment of the much more common condition, late-onset atherosclerotic cardiovascular disease [6]. We certainly hope that an understanding of the early-onset, genetic disease, DS, will provide insights into the therapy of the more common, late-onset AD. After all, the amyloid precursor protein (APP) and its cleavage by beta and gamma secretases with subsequent aggregation of Abeta monomers into soluble Abeta oligomers that, in turn, form insoluble fibrils found in amyloid plaques occurs both in AD and in DS. However, recent studies suggest that this thesis may not be so simple.

An important step in developing a therapy for AD has been the creation of an animal model of the disease. A murine model of AD was developed by Games et al. by introducing into the mouse genome a human, mutant APP gene from a patient with early-onset, genetic AD [7]. These transgenic mice develop cerebral amyloid plaques and impaired cognition and mimic, in many ways, human AD. Using this model, Schenk and his colleagues showed that active immunization of 3 week old APP transgenic mice with Abeta prevented the subsequent development of amyloid plaques and abrogated cognitive impairment [8,9]. If Abeta immunization of APP transgenic mice were not begun until 11 months of age, the number of Abeta plaques and the cognitive deficits were only partially decreased by such treatment.

The results of active immunization of APP-transgenic mice with Abeta encouraged similar therapy in patients with AD. Unfortunately, the initial clinical trial of active Abeta immunization of patients with AD had to be interrupted because T-cell-mediated encephalitis developed in a small number of the AD patients who had been immunized [10]. However, examination of the brains from AD patients actively immunized with Abeta, who later died of causes unrelated to Abeta immunization, showed a marked reduction in the number of cerebral Abeta plaques [11]. Despite this encouraging finding, there was no evidence of improved cognitive function in AD patients during or after active immunization. These studies suggested the importance of initiating anti-AD therapy early in the disease process, before neuronal loss has been too great to allow the recovery of cognitive loss.

Many investigators felt that passive immunotherapy with anti-Abeta antibodies would be safer than active immunization. Passive immunization had been proven effective and safe in the APP-transgenic mouse model of AD and would avoid the risk of activating human T cells that provoked immune encephalitis [12]. Additional support for passive immunization of patients with AD stemmed from the observation that the levels of natural anti-Abeta antibodies in plasma and cerebrospinal fluid of patients with AD were lower in patients with AD compared to age-matched controls [13]. This finding raised the possibility that having low levels of anti-Abeta antibodies increased the risk of AD, so that infusion of anti-Abeta antibodies might decrease the levels of Abeta and, thereby, benefit patients with AD.

Studies were begun in the USA and Europe by infusing preparations of human IgG (IVIg) purified from plasma from healthy, young, individuals with high titers of anti-Abeta antibodies into AD patients. Infusions of IVIg did result in increased levels of anti-Abeta antibodies and of Abeta in the plasma of patients with AD and decreased levels of Abeta in cerebrospinal fluid (CSF) [14]. However, it was not yet clear whether increased clearance of Abeta in the CSF occurred in the phase III studies. In addition, pharmaceutical companies began producing humanized murine monoclonal anti-Abeta antibodies for the treatment of patients with AD. Encouraging results from phase I and II studies were reported in AD patients treated with either IVIg or humanized monoclonal anti-Abeta antibodies.

However, two pharmaceutical giants, Johnson and Johnson as well as Pfizer, reported on August 6, 2012, that their jointly developed, humanized monoclonal anti-Abeta antibodies (Babineuzumab) had failed to show significant benefits in phase III trials in patients with AD. The two companies announced that they would not pursue further studies of these anti-Abeta antibodies. The executives of the third pharmaceutical company, Eli Lily, which is said to have spent a billion dollars on their human monoclonal anti-Abeta antibodies (Solanezumab), will report their results at the end of September 2012 but warned that a successful outcome for their drug would be a "longshot". The only other passive immunotherapy on the immediate horizon that had shown success against AD in early phase II trials is Baxter International's intravenous immunoglobulin product that is in a phase III trial that will be completed in December, 2012 with results expected to be reported in early 2013.

In the meantime, considerable progress is being made in determining the rate of production and clearance of Abeta in the pathogenesis of AD. Techniques have now been developed to determine the rate of Abeta production and Abeta clearance from the CNS in experimental animals as well as in normal humans and patients with AD using Abeta peptides labeled with stable isotope [15]. The average clearance rate of Abeta40 or Abeta42 was 30% lower in patients with AD than in healthy controls although the production of either Abeta40 or Abeta42 did not differ between healthy humans and patients with AD [16]. The E4 haplotype of apolipoprotein E is known to be the most important risk factor for AD in contrast to apolipoproteins E2 and E3, which are associated with a decreased risk of developing AD. AD patients expressing the apolipoprotein E4 gene have a slower clearance of Abeta from the CNS than do AD patients expressing apolipoprotein E2 or E3 genes.

Using these clearance techniques in mice, it was shown that clearance of Abeta from the brain into the peripheral circulation was critically dependent upon apolipoprotein E [17]. Thus, apolipoprotein E-mediated clearance of Abeta from the CNS could also be increased by 25% for as long as 3 days by a single oral dose of bexarotene given to 2 month-old APP-PS1 transgenic mice. Bexarotene treatment was also effective in 11 month old mice where one week's treatment decreased soluble and insoluble Abeta levels in the brain by 50% with a parallel reduction in amyloid plaque numbers. Finally, the same authors also presented persuasive evidence that 3 months of treatment