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Review

Animal systems in the development of treatments for Alzheimer's disease: challenges, methods, and implications

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Abstract

Substantial resources and effort have been invested into the development of therapeutic agents for Alzheimer's disease (AD) with mixed and limited success. Research into the etiology of AD with animal models mimicking aspects of the disorder has substantially contributed to the advancement of potential therapies. Although these models have shown utility in testing novel therapeutic candidates, large variability still exists in terms of methodology and how the models are utilized. No model has yet predicted a successful disease-modifying therapy for AD. This report reviews several of the widely accepted transgenic and nontransgenic animal models of AD, highlighting the pathological and behavioral characteristics of each. Methodological considerations for conducting preclinical animal research are discussed, such as which behavioral tasks and histological markers may be associated with the greatest insight into therapeutic benefit. An overview of previous and current therapeutic interventions being investigated in AD models is presented, with an emphasis on factors that may have contributed to failure in past clinical trials. Finally, we propose a multitiered approach for investigating candidate therapies for AD that may reduce the likelihood of inappropriate conclusions from models and failed trials in humans.

Keywords: Alzheimer's disease; Transgenic; Drug development; Review

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss, decline in cognitive function, and eventual death. It is the most common cause of dementia with more than 34 million people worldwide currently affected. Prevalence rates are expected to increase as the percentage of individuals over the age of 65 rises (Ferri et al., 2005). Approximately $420 billion was spent on care of AD patients worldwide in 2009 (Wimo et al., 2010). The financial burden imposed by this disorder as well as the stress on caregivers and family members represents a major global threat. Current pharmacological interventions for AD have symptomatic benefits but do not prevent or delay progressive neurodegeneration. Many promising new therapeutic approaches are being developed that address the fundamental neurobiology of AD and may have disease-modifying effects.

Agents targeting aspects of the neurobiology of AD in the quest to develop disease-modifying treatments are nearly universally tested in animal models of AD prior to being advanced to human testing in clinical trials. The US Food and Drug Administration (FDA) mandates toxicity testing in animals and most programs developing new agents also seek efficacy data in animal models. A wide variety of animal models have been employed to investigate treatment efficacy. Aged rodents and nonhuman primates provide models of human aging, transgenic species carrying amyloid precursor protein (APP), presenilin (PS), or tau mutations are used to assess effects on amyloid-beta protein (Aß) or tau protein metabolism, and other wild type and transgenic species help explore specific disease pathways and the effects of therapeutic interventions. While no animal model has been validated by predicting human clinical benefit for a disease-modifying compound, the widespread use of animal models in drug development programs requires a

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comprehensive understanding of their roles and limitations in therapeutic testing.

The plethora of animal models relevant to AD creates questions regarding the consistency across models and the predictive value of different models for human efficacy. Animal model systems currently serve a dual role, both in the identification of mechanisms responsible for the disorder and as a test bed for novel therapeutic development. This duality may complicate the interpretation of data for potential treatments. From the outset, an understanding of the role of model systems for disease state investigations versus testing of novel therapeutics should be made. This approach may lead to a more uniform adoption of specific models as the most appropriate for testing novel therapeutics. It may also allow alternative animal models to continue to elucidate mechanisms responsible for the disorder.

Reasonable promise of efficacy is desirable prior to investing the time, effort, and funds to advance to human testing and the expectation of efficacy is critical prior to exposing healthy controls and AD patients to potential side effects associated with therapeutic testing. In this report we review selected animal models and address questions relevant to efficacy assessments in animal models prior to human clinical trials. We suggest a sequential plan for garnering sufficient animal data which may be beneficial to the success of agents transitioning into clinical trials.

2. Animal models with Aß pathology

Several animal models of AD have been developed which exhibit one or more of the pathological hallmarks of the disorder such as Aß deposition or tau hyperphosphorylation. Cognitive deficits are also present in many models and can provide insight into core deficits and the effects of therapy on learning and memory. A host of different species, including mice, rats, flies, fish, rabbits, dogs, guinea pigs, and nonhuman primates, have been utilized to model AD pathologies with varying success. The diversity of current animal models can be used to facilitate the discovery of novel therapeutics and provide insights into the etiology of AD. The most widely utilized models are transgenic mice and we discuss them in greatest detail.

Initial transgenic mouse lines developed to study AD carried familial mutations of APP (Games et al., 1995; Hsiao et al., 1996), while subsequent models have relied on PS mutations (Duff et al., 1996), tau mutations (Lewis et al., 2000), or a combination of 2 or 3 mutations (Holcomb et al., 1998; Lewis et al., 2001; Oddo et al., 2003).

The first animal model to show Aß aggregation and plaque development was the PDAPP mouse which carries the Indiana mutation (V717F) of APP (Games et al., 1995). These mice develop plaques by the age of 6–9 months, an event preceded by deficits in synaptic function. They also display an increase in tau hyperphosphorylation, but neurofibrillary tangles (NFTs) are absent. A subsequent model, the Tg2576 mouse, was developed by insertion of the Swedish double mutation (K670N and M671L) and a similar phenotype to the PDAPP mice was observed (Hsiao et al., 1996). The Tg2576 mice display cognitive impairments and plaque deposition at 9 months of age. Substantial neuronal loss is not a feature of this model, a significant difference from human AD. These mice have been used frequently to examine the therapeutic potential of a host of novel compounds and are the most widely used model to test evolving therapeutics for AD. While this mouse has extensive amyloid deposits, the amyloid appears to be less aggregated than human plaque amyloid (Kalback et al., 2002) and may be more amenable to mobilization than typical human Aß deposits.

The APP23 mouse model also expresses the Swedish double mutation but in an alternatively spliced isoform of APP (Sturchler-Pierrat et al., 1997). APP23 mice show plaque deposition and hyperphosphorylated tau by 6 months of age as well as cerebral amyloid angiopathy (CAA). Progressive, age-related cognitive impairments are observed in these mice starting as early as 3 months of age before amyloid deposits form (Van Dam et al., 2003); increased levels of soluble Aß may be responsible for these deficits. Significant neuronal loss, a characteristic feature of AD, has also been observed in APP23 mice at 14–18 months of age within hippocampal regions (Calhoun et al., 1998).

Another model that relies on mutations in the APP gene is the J20 mouse. The Swedish double mutation was inserted into the PDAPP mice creating a triple mutant mouse with faster and more aggressive Aß accumulation and plaque deposition (Mucke et al., 2000). Synaptic loss and cognitive deficits appear early in these mice (between 2 and 4 months of age) while amyloid deposition occurs by 6 months. J20 mice display deficits in synaptic plasticity as well as neuronal network hyperexcitability, a phenomenon which has also been observed in AD patients (Palop et al., 2007).

Mutations in PS genes lead to increased production of Aß and a disproportionate production of $Aß_{42}$ over $Aß_{40}$ with enhanced Aß aggregation and neurotoxicity. The first animal model to be developed with a mutation in the PS gene was the PS1 mutant mouse which carries the M146L mutation of PS1 (Duff et al., 1996). These mice display an increased ratio of $Aß_{42}/Aß_{40}$ and display impaired intracellular calcium regulation (Barrow et al., 2000). However, PS1 mice do not display prominent amyloid plaque deposition or learning and memory impairments (Janus et al., 2000).

Combining PS and APP mutations results in mice that display large amounts of aggregated Aß at an early age. PSAPP mice are a cross of the Tg2576 transgenic line and the PS1 mice (Holcomb et al., 1998). They display plaque deposition at an earlier age than the singly transgenic Tg2576 mice along with large increases in $Aß_{42}$ levels. Further, cognitive deficits appear before the presence of amyloid pathology. Expanding on this double transgenic animal, the 5XFAD mice were created with 3 mutations in