Ageing Research Reviews 12 (2013) 116–140

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Drug pipeline in neurodegeneration based on transgenic mice models of Alzheimer's disease

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ARTICLE INFO

Article history:
Received 16 April 2012
Received in revised form 31 August 2012
Accepted 4 September 2012
Available online 12 September 2012

Keywords:
Transgenic mice
Alzheimer's disease
Anti-Alzheimer therapeutics

ABSTRACT

Alzheimer's disease (AD) is one of the most important neurodegenerative disorders, bringing about huge medical and social burden in the elderly worldwide. Many aspects of its pathogenesis have remained unclear and no effective treatment exists for it. Within the past 20 years, various mice models harboring AD-related human mutations have been produced. These models imitate diverse AD-related pathologies and have been used for basic and therapeutic investigations in AD. In this regard, there are a wide variety of preclinical trials of potential therapeutic modalities using AD mice models which are of paramount importance for future clinical trials and applications. This review summarizes more than 140 substances and treatment modalities being used in transgenic AD mice models from 2001 to 2011. We also discuss advantages and disadvantages of each model to be used in therapeutic development for AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia among the aging population (Bertram and Tanzi, 2008). The disease has been the sixth leading cause of death across all ages and the fifth leading cause of death for those aged 65 and older (Arialdi et al., 2010; Wimo et al., 2003).

AD is a multifactorial disease, clinically characterized by progressive cognitive loss, neuropsychiatric and behavioral disorders. Pathological findings include extracellular amyloid beta (Aβ) plaques in brain parenchyma and arterioles, intracellular neurofibrillary tangles (NFTs), the loss of neuronal subpopulations, mitochondrial oxidative damage, synaptic loss, proliferation and activation of astrocytes and microglia (Mattson, 2004; Reddy et al., 2010; Selkoe, 2001).

According to current theories, Aβ accumulation and tau hyperphosphorylation are considered the core pathologies of AD (Hardy and Allsop, 1991; Selkoe, 2000). Excessive Aβ accumulation, as a result of either increased production or decreased clearance, leads to the formation of senile plaques (SPs) (Selkoe, 2000). Thereafter, a series of biological events starts which ends up with an impairment of neuronal synapses and dendrites through oxidative stress and inflammatory processes (Heneka and O'Banion, 2007; Roberson

Abbreviations: 7,8-DHF, 7,8-dihydroxyflavone; Aβ, amyloid beta; AchE, acetylcholine-esterase; ABCA1, ATP-binding cassette transporter 1; APP, amyloid precursor protein; Akt, protein kinase B; ApoE, apolipoprotein E; AAV/Aβ, adeno-associated viral vector carrying Aβ cDNA; BACE1, β-site APP-cleaving enzyme 1 gene; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BM-MSCs, transplantation of bone marrow-derived mesenchymal stem cells; CAST, calpastatin; CBL, cerebrolysin; Cdk5, cyclin-dependent kinase 5; ChEIs, cholinesterase inhibitors; CSF, cerebro-spinal fluid; Compound A, 6-methyl-N-[3-[[3-(1-methylethoxy)propyl]carbamoyl]-1H-pyrazol-4-yl]pyridi ne-3-carboxamide; CoQ 10, coenzyme Q10; CREB, cAMP response element-binding; CQ, clioquinol; CTF, carboxyterminal fragments; CTS, cryptotanshinone; DAPT, N-[30]-S-phenylglycine t-butylester; DM, dextromethorphan; DHA, docosahexaenoic acid; DHT, dihydrotestosterone; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; ETC, electronic transport chain; EPO, erythropoietin; FAD, familial Alzheimer's disease; FDA, food and drug administration; FTDs, frontotemporal dementias; GFAP, glial fibrillary acidic protein; GLT-1, glutamate transporter-1; GSPE, grape seed polyphenolic extract; GM-CSF, granulocyte-macro-phage-colony stimulating factor; GSIs, γ-secretase inhibitors; GSMs, γ-secretase modulators; GSK-3, glycogen synthase kinase 3; G-CSF, granulocyte colony-stimulating factor; Gtsm, compound Cu(II); Hcy, homocystine; HDAC, histone deacetylase; HNG, S14G-Humanin; IDE, insulin-degrading enzyme; IMX, indirubin-3′-monoxime; IVIG, purified intraveneous immunoglobulin; KKT, kami-kihi-to; L-DOPS, l-threo-3,4-dihydroxyphenylserine; L-NBP, l-3-n-butylphthalide; LTP, long-term potentiation; MARK, microtubule-associated regulatory kinase; MCAT, mitochondria-targeted antioxidant catalase; NMDA, N-methyl-D-aspartic acid; NFTs, neurofibrillary tangles; NSAIDs, non-steroidal anti-inflammatory drugs; nAChRs, nicotinic acetylcholine receptors; PAC, P1-derived artificial chromosome; PJ, pomegranate juice; SAM, S-adenosyl methionine; sAPPα, secreted amyloid precursor protein-α; SP, senile plaque; T2DM, type 2 diabetes mellitus; Tau/tCr, taurine/creatine; Tg, transgenic; PBN, α-phenyl-N-tert-butyl nitrone; PDTC, pyrrolidine dithiocarbamate; PPF, propentofylline; PKC, protein kinase C; PS, presenilin; VAβ, vascular Aβ; VPA, valproic acid.

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http://dx.doi.org/10.1016/j.arr.2012.09.002

and Mucke, 2006). NFTs, another pathological hallmark of AD, consist of abnormally hyperphosphorylated tau protein, and contribute to fulminant brain degeneration and disease progression (Iqbal et al., 2009). Mitochondrial dysfunction and abnormal mitochondrial dynamics are further accompanying events that contribute to the cognitive deficits and synaptic damage (Manczak et al., 2006, 2010; Reddy et al., 2010, 2004; Zhao et al., 2010). Activation and proliferation of brain glial cells, such as astrocytes and microglia will finally add up to the pathology of CNS through production of pro-inflammatory cytokines and toxins related to neurodegenerative process (McGeer and McGeer, 2002). AD-associated vasculopathy and vascular Aβ (VAβ), is another common aspect of AD which has been focused in recent years (Viswanathan and Greenberg, 2011). The blood–brain barrier (BBB) is thought to be disrupted as a result of amyloid deposition in vessels and lead to a passage of proteins in cerebro-spinal fluid (CSF), causing a cascade of immune responses and damage to the brain (Sardi et al., 2011).

Considering the substantial financial and social costs of neurodegenerative diseases, development of therapeutics against AD is an emergent need and many transgenic mouse models have been established to focus on the major aspect of AD: the proteinopathies of Aβ and tau. In these models, many compounds and other therapeutic strategies were studied with surprising success.

In this review, we comprehensively summarize the main transgenic mice models of AD along with relevant preclinical drug trials for each transgenic mouse strain.

2. Major transgenic mice models of AD

More than 95% onsets of AD occur later than 65 years which are called "sporadic" AD while less than 5% of AD cases accounts for early-onset autosomal dominant forms, called familial AD (FAD) (Beach, 2008). Current AD research mainly depends on the later form of disease. Two reasons can be mentioned for this situation. First of all, FAD fully represents amyloid theory which is the best known and accepted theory describing molecular mechanisms of AD (Hardy and Allsop, 1991). Secondly and most importantly, transgenic models could be designed from involved genes in familial forms which are of foremost importance for investigational purposes. So far, three different genes have been described in relation to FAD, namely the amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) gene (Bertram and Tanzi, 2012). Their variations are known to be responsible for Aβ accumulation (Bertram et al., 2010; Citron et al., 1997; Scheuner et al., 1996). Transgenic mice models are capable of recapitulating main pathological features of disease in human beings (Chin, 2011).

However, due to the complexity of disease, it was difficult to create transgenics (tg) that exhibit the intricate characteristics of AD. As a result, each produced tg mice could only represent certain pathological, physiological, or behavioral features of the human disease (Chin, 2011). Getting to know these specificities in each tg mice is important, since such specifications determine the appropriate investigational application of various mice models.

2.1. Transgenic mice harboring APP mutations

As mentioned before, the amyloid hypothesis mainly emphasizes on excessive Aβ production as the core pathology of AD (Hardy and Allsop, 1991). Besides, the presence of defined genes responsible for FAD has assisted making AD models overexpressing APP. These APP tg mice represent major pathological features of AD, including parenchymal and vascular amyloid pathology, plaque-associated dystrophic neuritis, microglial activation, synaptic impairments, and learning and memory deficits (Chishti et al., 2001; Games et al., 1995; Hsiao et al., 1996; Sturchler-Pierrat et al., 1997). Transgenic mice expressing APP mutations have been most widely used for drug evaluation.

2.1.1. PD-APP transgenic mice

PD-APP tg mice has been the first successful AD transgenic mice harboring the human APP695swe with APP717V-F sequence (Games et al., 1995). This model generates up to 18-fold increase in APP RNA and about 4–6 times of human APP protein (Games et al., 1995). Several experimental therapeutic interventions, like immunotherapy, epigenetic modulation, gene delivery, and others, have been investigated with these mice.

In PD-APP tg mice, neuropathological changes progress along with increasing age. There are no major pathological changes prior to 6 months. At 6–9 months of age, the animals start to exhibit Aβ deposits in the hippocampus, corpus callosum and cerebral cortex. The density of plaques would increase to 20–50% of the neuropil (Games et al., 1995). Neuritic alterations and astrogliosis would rapidly emerge around dense core plaques (Games et al., 1995). Behavioral features include overexcitation (3rd month), changes in sleep wake-up mode (3–5th month) (Huitron-Resendiz et al., 2002), decreased spontaneous object recognition (appearing at 6 months of age and aggravates with increasing amyloid deposition) (Dodart et al., 1999), and spatial memory deficits (13th month) (Chen et al., 2000). Although cytoskeletal abnormalities, tau hyperphosphorylation emerges, no neurofibrillary tangles and paired helical filaments develop. Using this model, 15 substances belonged to passive immune therapies, gene delivery and so on are discovered in preclinical trials and listed. (Table 1)

2.1.2. Tg2576 transgenic mice

Tg2576 mice harbor mutant human APP695 with double mutations at KM670/671NL (Hsiao et al., 1996). These mice produce 5–6 times higher levels of human APP as compared to the endogenous mice APP. Considering the more comprehensive representation of amyloid pathology, this model has been more widely used in preclinical investigations than PD-APP mice (Table 2).

Abnormal mitochondrial gene expressions and oxidative damage are the first events in Tg2576 that occur even before the Aβ appearance (Manczak et al., 2006; Reddy et al., 2004). An N-terminal signal in the APP molecule enters mitochondria via positively charged residues of APP molecule at 40, 44 and 51(Anandatheerthavarada et al., 2003). It would disrupt the electronic transport chain (ETC) leading to the free radicals induction, oxidative damage and further mitochondrial dysfunction (Mao et al., 2012). Double-transgenic mouse line MCAT/APP was produced through cross breading of MCAT mice with Tg2576 (Mao et al., 2012). These mice carried human mitochondria-targeted antioxidant catalase (MCAT) gene and lived 5 month more than Tg2576 showing reduced levels of APP, carboxyterminal fragments (CTF)99, β-site APP-cleaving enzyme 1 gene (BACE1), Aβ42, Aβ40, Aβ deposits and oxidative DNA damage and increased soluble APPα and CTF83 (Mao et al., 2012). This confirms the significant role of mitochondrial dysfunction in Tg2576 mice.

Enhanced Aβ production is found at 2 months of age. Aβ accumulates with age and excessive Aβ can be detected at 4–5 months. Amyloid plaques gradually deposit in the frontal and temporal lobes, entorhinal cortex, hippocampus and cerebellum and by 12 months, diffuse plaques are evident (Kawarabayashi et al., 2001). As soon as Aβ deposits in the CA1 region of the hippocampus and the number of microglial cells increase, learning and memory impairment would occur. This happens around 9 months of age.

Although both PDAPP and Tg2576 models overexpress APP, there is a set of differences between these two. The ratio of $A\beta_{40}/A\beta_{42}$ peptide is equivalent in Tg2576 mice, while PD-APP mice exhibit an extraordinary increase of $A\beta_{42}$ levels (Fryer et al., 2003; Hsiao et al., 1996). Besides, age-associated memory