Brain Research Bulletin 110 (2015) 26–29

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Review

Medical genetics-based drug repurposing for Alzheimer's disease

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ARTICLE INFO

Article history:
Received 8 August 2014
Received in revised form
12 November 2014
Accepted 13 November 2014
Available online 22 November 2014

Keywords:
Alzheimer's disease
Medical genetics
Drug repurposing
Angiotensin-converting enzyme inhibitors

ABSTRACT

Alzheimer's disease (AD) is a disease that threatens the elderly. No efficient therapeutic method is currently available to combat AD. Drug repurposing has provided a new route for AD drug discovery, and medical genetics has shown potential in target-based drug repurposing. We compared AD-associated genes with approved drug targets and found that three are targeted by 23 approved drugs. Thus, these drugs may be used to treat AD according to the medical genetic information of the targets. In vitro and in vivo experiments revealed that four drugs, all of which are angiotensin-converting enzyme (ACE) inhibitors, had potential to treat AD.

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Contents

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to dementia among the elderly. The prevalence rate of AD increases in an age-dependent exponential manner after the age of 65; this rate may reach 30% at the age of >90 (Brookmeyer et al., 2011). More than 66 million people are estimated to have dementia worldwide by 2030 and 115 million by 2050. AD incurs an enormous global cost, which reached US $604 billion in 2010; this value will increase in proportion to the number of people with dementia (Wimo and Prince, 2011).

Many efforts have been exerted to treat AD (Danilova et al., 2014; Dias Fiuza Ferreira et al., 2013; Varga et al., 2014; Yulug et al., 2014). However, little progress has been achieved in AD drug discovery in the past decade. Currently available drugs are still cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, all of which exhibit limited clinical efficacy (Helmuth, 2002). Thus, developing effective therapies for AD is urgently needed. Drug repurposing, the application of approved drugs for new therapies, has provided a new route for AD drug discovery in recent years (Cummings and Zhong, 2014; Appleby and Cummings, 2013); this approach can accelerate drug development process and reduce risks (Ashburn and Thor, 2004). Routine repurposing approaches include phenotype-based screening method, target-based method, knowledge-based method, signature-based method, pathway- or network-based method, and targeted mechanism-based method (Jin and Wong, 2014).

Abbreviations: AD, Alzheimer's disease; GOF, gain of function; LOF, loss of function; MoA, mode of action; TTD, Therapeutic Target Database; Aβ, amyloid-β; ROS, reactive oxygen species; ACE, angiotensin-converting enzyme; APP, amyloid-protein precursor; ACEi, ACE inhibitors; HUVECs, human umbilical vein endothelial cell; PPAR-γ, peroxisome proliferator-activated receptor gamma.

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http://dx.doi.org/10.1016/j.brainresbull.2014.11.003
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Phenotypic screening or target-based method has revealed several promising anti-AD drug candidates, such as angiotensin receptor blockers, calcium channel blockers or glucagon-like peptide 1 analogs, tetracycline antibiotics, and retinoid X receptor agonists (Corbett et al., 2012; Corbett and Ballard, 2013). Wang and Zhang (2013) have recently indicated that the medical genetics of drug targets can provide useful information to predict new activities and side effects of approved drugs, thereby providing a new route to perform anti-AD drug repurposing.

2. Medical genetics-based anti-AD drug repurposing

Drug targets are usually disease-causing genes because of a common feature in which phenotypes are closely linked with genotypes (Wang et al., 2012a). The pathogenesis of genetic diseases can be classified into two mechanisms, namely, through gain of function (GOF) and loss of function (LOF) mutation of disease-causing genes. Therefore, the drug mode of action (MoA) must match the pathogenesis. That is, the potential drugs for a target connecting to a genetic disease caused by GOF (or LOF) mutation must be inhibitors/antagonists (or agonists) of the target. Otherwise, the drugs will not elicit therapeutic effects but adverse effects (Brinkman et al., 2006). However, one gene may corresponds to multiple genetic diseases because of gene pleiotropy; thus, new indications and side effects of known drugs can be predicted by combining the genetic characteristics of the targets and the drug MoA (Wang and Zhang, 2013; Wang et al., 2014). The present study attempts to use this method to find potential anti-AD drugs.

Wang et al. (2012b) have recently identified 3949 human disease genes from Online Mendelian Inheritance in Man (OMIM) and Human Gene Mutation Database (HGMD), in which 37 genes are associated with AD. We compared these genes with 498 successful human drug targets collected from literature and Therapeutic Target Database (TTD) (Wang et al., 2012a) and found three (IDE, ACE, and NOS3) are drug targets, all of which have GOF annotations in OMIM. Although there are other databases containing AD genetic association information, such as AlzGene database (Bertram et al., 2007), they do not provide GOF/LOF information for the genes and thus were not used in the present drug-repurposing research. However, the three AD-associated genes (IDE, ACE, and NOS3) are indeed recorded in AlzGene. In particular, ACE is among the most strongly AD-associated genes. As recorded in TTD, 23 approved drugs target these genes, all of which are inhibitors (Table 1). The 23 drugs are principally used to treat cardiovascular diseases and hypertension but may also be used to treat AD according to the medical genetic annotations of the targets. Four ACE (angiotensin-converting enzyme) inhibitors (captopril, enalapril, lisinopril, and perindopril) have been revealed as anti-AD agents by in vitro and in vivo observations (Ohrui et al., 2004a,b; Shah et al., 2009; AbdAlla et al., 2013; Yamada et al., 2010; Dong et al., 2011; Yang et al., 2013). The possible anti-AD pharmacological mechanisms of these ACE inhibitors are summarized below.

3. Anti-AD pharmacological mechanisms of ACE inhibitors

ACE regulates blood pressure by cleaving angiotensin I to angiotensin II and inactivating bradykinin (Coates, 2003). Human genetic and pathologic studies have associated ACE with AD. Either single nucleotide polymorphisms (Katzov et al., 2004) or an intronic insertion (I)/deletion (D) polymorphism within the ACE gene is associated with AD. The D allele is associated with a reduced risk for AD, whereas heterozygotes are at increased risk (Lehmann et al., 2005). In addition, ACE activity is enhanced in certain brain regions of AD patients (Arregui et al., 1982; Barnes et al., 1991; Singh et al., 2013). In vitro studies showed that ACE promotes amyloid-β (Aβ)40 and Aβ42 degradation, whereas ACE inhibitors captopril and lisinopril block this effect (Savaskan et al., 2001; Hemming and Selkoe, 2005). ACE inhibitors are common antihypertensive medications. Thus, whether or not ACE inhibitors can elevate Aβ level in vivo should be further studied. Hemming et al. (2007) confirmed that captopril cannot cause Aβ accumulation in aged amyloid-protein precursor (APP) transgenic mice. Moreover, brain-penetrating ACE inhibitors such as captopril and perindopril not only reduce the incidence of AD in elderly hypertensive patients but also slow cognitive decline in mild to moderate AD patients (Ohrui et al., 2004a,b). A systematic review suggests that ACE inhibitors reduce the incidence and progression of dementia in AD and vascular dementia patients (Shah et al., 2009). More recently, several clinical researches found that centrally acting ACE inhibitors, especially perindopril, are associated with a reduced decline in cognition in patients with mild to moderate AD, compared with other antihypertensive drugs or non-centrally active ACE inhibitors. It suggested that centrally acting ACE inhibitors may slow disease progression in AD (Soto et al., 2013; Gao et al., 2013; O'Caoimh et al., 2014).

Aβ can directly cause reactive oxygen species (ROS) production. ROS have been implicated in AD pathogenesis (Radak et al., 2011) and have become research targets in the prevention and treatment of AD. The angiotensin II AT1 receptor is also a major ROS source, and high ACE levels in AD brain account for angiotensin-induced ROS generation (AbdAlla et al., 2013). Recent studies have shown that captopril retards neurodegeneration in AD mice by decreasing hippocampal ACE activity, consequently reducing ROS level and APP processing (AbdAlla et al., 2013).

Growing evidence demonstrates that angiotensin II is a crucial mediator of AD pathology. It promotes β amyloid production via binding angiotensin II type 1 receptor in rats (Zhu et al., 2011), and induces tau phosphorylation and cognitive impairment in normal rat brains (Tian et al., 2012). Moreover, it increases ROS (Zimmerman et al., 2002) and inflammation in central neural system, action as an endogenous pro-inflammatory molecule (Das, 2005). Angiotensin receptor blockers reduce the angiotensin II-mediated inhibition of acetylcholine release and consequently improve cognitive function, showing neuroprotective effects against AD. ACE inhibitors exhibit similar effects by reducing angiotensin II production (Kehoe and Wilcock, 2007). For instance, perindopril reverses cognitive impairment in Aβ25–35-induced mice and PS2APP-transgenic mice by inhibiting brain ACE activity (Yamada et al., 2010; Dong et al., 2011). The neuroprotective effect of perindopril is associated with the suppression of hippocampal astrocyte activation and the attenuation of superoxide (Dong et al., 2011). Perindopril also improves cognitive impairment in the D-galactose and aluminum trichloride-induced AD mouse model by inhibiting acetylcholinesterase and oxidative stress (Yang et al., 2013).

AD involves synaptic dysfunction, energy and lipid metabolism perturbation, and microglial-mediated inflammatory response caused by amyloid plaques. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-activated transcription factor that regulates glucose and lipid metabolism, and suppresses inflammatory gene expression. Thus, PPAR-γ agonists have been regarded as new therapeutic targets in AD treatment (Landreth et al., 2008). Interestingly, the ACE inhibitor lisinopril can attenuate learning and memory impairment in the streptozotocin-induced AD mouse model by activating PPAR-γ (Maxwell and Hogan, 2010; Singh et al., 2013).

New concepts regarding the role of endothelial cells, vascular disease, and oxidative stress in AD pathogenesis have recently emerged (Casado et al., 2008). Endothelial dysfunction is linked with vascular disease and neuroinflammatory diseases, which

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