Pharmacology & Therapeutics 172 (2017) 22–33

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Prion-like mechanisms and potential therapeutic targets in neurodegenerative disorders☆

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ARTICLE INFO

Available online 1 December 2016

Keywords:
Alzheimer's disease
Parkinson's disease
ALS
Tau
α-synuclein
TDP-43

ABSTRACT

Prion-like propagation of abnormal intracytoplasmic proteins, which are the defining features of major neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), has been proposed. A growing body of evidence strongly suggests that abnormal tau, α-synuclein and TDP-43 have prion-like properties, convert the corresponding normal proteins into abnormal forms, and are transmitted from cell to cell, spreading throughout the brain. This idea is extremely important not only for understanding the pathogenesis and progression of these diseases, but also for the development of molecular therapies. Since the distributions and spreading of the abnormal proteins are closely associated with disease symptoms and progression, gain-of-toxic-function of these proteins may affect the neurons and glial cells either directly or indirectly, or both. It is essential to regulate the aggregation of abnormal intracellular proteins and their cell-to-cell transmission in order to stop, or at least slow, the progression of these diseases.

Contents

1. Introduction

Neurodegenerative diseases are characterized by progressive degeneration of subsets of neurons and gliosis. Many of these disorders are accompanied with distinct pathologies in the central nervous system, consisting of abnormal proteinaceous structures: neurofibrillary tangles in Alzheimer's disease (AD), Lewy bodies in Parkinson's disease (PD) and skein-like inclusions in amyotrophic lateral sclerosis (ALS)(Fig. 1A–C). Since the 1980′s, attempts had been made to identify the components of these pathological structures in order to explore the molecular mechanisms of neurodegeneration and the pathogenesis of the diseases. A microtubule-associated protein, tau, was discovered to be the major component of neurofibrillary tangles in the mid-1980′s (Brion, Flament-Durand, & Dustin, 1986; Delacourte & Defossez, 1986; Grundke-Iqbal et al., 1986; Kosik, Joachim, & Selkoe, 1986; Nukina & Ihara, 1986). α-Synuclein (αSyn) was found to be the protein component of Lewy bodies in PD and dementia with Lewy bodies (Spillantini et al., 1997; Baba et al., 1998; Spillantini, Crowther, Jakes, Hasegawa, & Goedert, 1998). Also, TAR DNA binding protein of 43 kDa (TDP-43) was identified as a component of intracellular ubiquitin-positive

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; ALS, amyotrophic lateral sclerosis; αSyn, α-synuclein; TDP-43, TAR DNA binding protein of 43 kDa; FTLD, frontotemporal lobar degeneration; PrP(C), normal prion protein; PrP(sc), abnormal prion protein; TTR, transthyretin.

☆ This work was supported by Ministry of Education Japan Society for the Promotion of Science KAKENHI Grant 23228004 (to M. H.), Ministry of Health, Labor, and Welfare of Japan Grant 12946221(to M. H.), grant-in-aid for research on rare and intractable diseases, the Research Committee on Establishment of Novel Treatments for Amyotrophic Lateral Sclerosis, and the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from Japan Agency for Medical Research and Development, AMED (to M. H.)

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http://dx.doi.org/10.1016/j.pharmthera.2016.11.010
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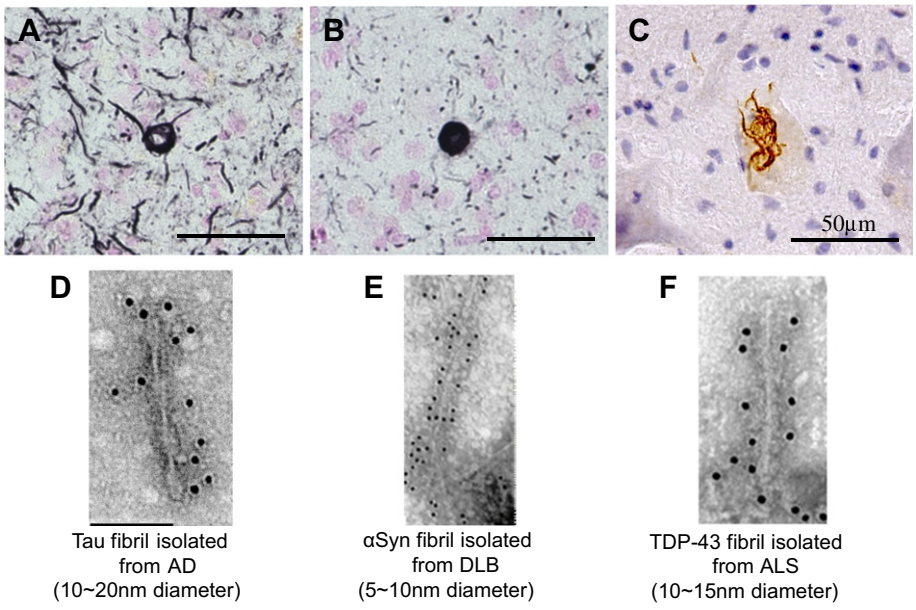

Fig. 1. Intracellular abnormal protein pathologies in major neurodegenerative diseases and electron microscopy of the isolated abnormal fibrils. A: Neurofibrillary tangles and threads in neocortex of AD (stained with an anti-phospho tau antibody AT8), B: Lewy bodies and Lewy neurites in neocortex of DLB (stained with an anti-phospho αSyn antibody, PS129), C: Skein-like inclusion in spinal cord of ALS (stained with an anti-phospho TDP-43 antibody, pS409/410). D: paired helical filament that constitutes the building block of tau pathologies in AD (stained with AT8, 10 nm gold particles). E: αSyn fibrils isolated from DLB brain (stained with PS129, 5 nm gold particles). F: TDP-43 fibrils isolated from brains of ALS patients (stained with pS409/410, 10 nm gold particles). Bar: 100 nm.

inclusions in ALS and frontotemporal lobar degeneration (FTLD)(Arai et al., 2006; Neumann et al., 2006). Immunocytochemical and biochemical studies using specific antibodies to the normal and abnormal proteins revealed widespread abnormal protein pathologies in these diseases (Fig. 1A–C), and the distributions and spread of the abnormal proteins were closely correlated with clinical presentation and disease progression. At an early stage of AD, tau pathology is observed in transentorhinal cortex, and at more advanced stages, widespread tau pathologies are seen in limbic regions and cortex (Braak & Braak, 1991; Braak & Del Tredici, 2011). In PD or DLB, αSyn pathology is detected in olfactory bulb, and/or dorsal motor nucleus in medulla at an early stage, and it is seen in amygdala, cholinergic nuclei of the basal forebrain and substantia nigra at later stages (Braak et al., 2003), or spread from the temporal lobe to the frontal lobe and further spread to the parietal and occipital lobes in DLB (Saito et al., 2003). It was also reported that TDP-43 pathology in ALS appears to disseminate in a sequential pattern that permits the recognition of 4 neuropathological stages consistent with the hypothesis that TDP-43 pathology is propagated along axonal pathways (Braak et al., 2013; Brettschneider et al., 2013; Brettschneider et al., 2014; Kassubek et al., 2014; Smethurst, Sidle, & Hardy, 2015), although these studies were done after the theory had been proposed. Thus, these diseases are "progressive" disorders, and the intracellular pathologies seem to spread during the course of the diseases. However, little attention had been given to the questions of why these diseases are progressive, and why the pathologies spread to different brain regions during the course of the diseases. This prion-like propagation is the principal molecular mechanism of these major neurodegenerative diseases with amyloid-like abnormal protein pathologies, and can account for the degeneration of subsets of neurons, the diverse but characteristic pathologies, and the disease progression (Brettschneider, Del Tredici, Lee, & Trojanowski, 2015; Frost & Diamond, 2010; Goedert, 2015; Halliday, Radford, & Mallucci, 2014; M. Hasegawa, 2016; Jucker & Walker, 2013; Prusiner, 2012). Therefore, regulation of the propagation of abnormal proteins is an important goal for disease-modifying therapy of these major neurodegenerative disorders.

2. Abnormalities in the pathological proteins found in neurodegenerative disorders

The pathological inclusions and their principal protein components (tau, αSyn and TDP-43)(Fig. 2) deposited in the brains of patients have been extensively studies by means of biochemical, immunochemical and protein chemical analyses. Although these proteins are different in size, structure (Fig. 2), subcellular localization and physiological functions, there are some common features (Table 1). Immunoelectron-microscopic studies demonstrated that the proteins accumulate as abnormal fibrils or filaments (Fig. 1D–E) with some cellular organelles, irregularly shaped structures and lipofuscins (M. Hasegawa et al., 2007; Lee, Balin, Otvos, & Trojanowski, 1991; Lin & Dickson, 2008; Spillantini, Crowther, Jakes, Cairns, et al., 1998; Spillantini, Crowther, Jakes, Hasegawa, et al., 1998). Most of these structures are Thioflavin S/T-positive (Delaere, Duyckaerts, Brion, Poulain, & Hauw, 1989; Hashimoto et al., 1998; Bigio et al., 2013), suggesting that the fibrils are amyloid-like and well-ordered, being clearly distinct from amorphous disordered aggregates. The term "amyloid-like" is used for intracellular proteins similar to amyloids, because the classical histopathological definition of "amyloid" is an extracellular, proteinaceous deposit exhibiting beta-sheet structure. All these abnormal proteins are sarkosyl-insoluble (Fujiwara et al., 2002; Greenberg & Davies, 1990; M. Hasegawa et al., 2008), and can be partially purified or enriched by utilizing this property in combination with ultracentrifugation. Mass spectrometric and immunohistochemical analyses revealed that these proteins deposited in brains are abnormally phosphorylated (Hasegawa et al., 1993; Morishima-Kawashima et al., 1995; Fujiwara et al., 2002; Hasegawa et al., 2008; Kametani et al., 2016), partially ubiquitinated (Morishima-Kawashima et al., 1993; Hasegawa et al., 2002; Kametani et al., 2016), deamidated and fragmented (Hasegawa et al., 1992; Arai et al., 2004; Hasegawa et al., 2011; Dan et al., 2013; Kametani et al., 2016; Taniguchi-Watanabe et al., 2016), in contrast to the situation in the brains of control cases. So, what is the most important feature for the pathogenesis among these abnormalities? Ubiquitination of αSyn