Ageing Research Reviews 26 (2016) 112–114

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Opportunities and challenges in developing relevant animal models for Alzheimer's disease

Fernanda G. De Felice [a,b,*], Douglas P. Munoz [b]

[a] Institute of Medical Biochemistry Leopoldo de Meis, Federal University of Rio de Janeiro, Rio de Janeiro, RJ 21944-590, Brazil
[b] Centre for Neuroscience Studies, Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario K7L 3N6, Canada

ARTICLE INFO

Article history:
Received 21 July 2015
Received in revised form
11 December 2015
Accepted 22 January 2016
Available online 30 January 2016

Keywords:
Alzheimer's disease
Animal models
Non-human primates

ABSTRACT

A major impediment to the development of safe and effective therapeutics in Alzheimer's disease (AD) lies in difficulties in translating research findings across species: therapies that work in rodents often do not translate to humans. A route to bridge the gap between promising rodent research and the human clinical condition consists in using non-human primates (NHPs), which are phylogenetically much closer to humans. In this article, we discuss the importance of investigating disease mechanisms from cell culture, through different animal models of disease. We highlight that developing a viable, validated NHP AD model will likely be a key step toward understanding AD-relevant pathogenic mechanisms and for developing therapies that will effectively translate to the human disease condition.

Contents

Currently, there is no effective treatment for Alzheimer's disease (AD) and the pursuit of novel disease-modifying therapeutics is the object of intense investigation. According to the ClinicalTrials.gov database, 1590 clinical trials testing hundreds of different compounds have been performed to date with AD patients (Table 1). Although a few therapeutic drugs (e.g., docosahexaenoic acid (Quinn et al., 2010)) and antibodies targeting the amyloid-β (Aβ) peptide (e.g., (Klyubin et al., 2005; Relkin et al., 2009)) have shown promise in preclinical studies and early clinical trials, most of the trials have been withdrawn/terminated (e.g., vaccine study) or failed to work in AD patients (Quinn et al., 2010). Indeed, of 244 unique compounds tested in humans since 2002, only memantine, an NMDA receptor antagonist, has safely translated into AD clinical practice, but with modest effectiveness in promoting cognitive improvement (Cummings et al., 2014). A major impediment to the development of safe and effective therapeutics arises from the difficulty to translate models of disease from one species to another. As a consequence, potential therapies that work in one species frequently fail to translate to humans.

Development of an animal model of AD that best approximates the human disease has been the goal of many researchers (LaFerla and Green, 2012; Selkoe, 2011). Information on mechanisms of AD pathogenesis and on preclinical evaluation of treatments directed at Aβ or phospho-tau has come from pathology, genetics, and various transgenic rodent models of AD (Goedert and Spillantini, 2006; LaFerla and Oddo, 2005; Yoshiyama et al., 2007). However, due to the complexity of the neuropathology spectrum of AD, such transgenic models are very useful for studying some, but not all, disease aspects. In fact, none of the available mouse models truly recapitulate the full spectrum of AD neuropathology (Selkoe, 2011), which includes Aβ deposition, synapse loss, inflammation, tau phosphorylation, and neurofibrillary tangle formation. In particular, a significant effort has been made to include tangle pathology in transgenic mice models of AD by including a mutation in tau (Oddo et al., 2003), which is associated with other tauopathies, such as frontotemporal dementia (Gotz and Ittner, 2008), but is not part of canonical AD pathology. The recent development of a transgenic rat model (TgF344-AD; expressing APP_{sw} and presenilin

* Corresponding author at: Institute of Medical Biochemistry Leopoldo de Meis, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil/Centre for Neuroscience Studies, Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Canada.
E-mail addresses: felice@bioqmed.ufrj.br (F.G. De Felice), doug.munoz@queensu.ca (D.P. Munoz).

http://dx.doi.org/10.1016/j.arr.2016.01.006
1568-1637/

Table 1
Number of clinical trials performed to date with AD patients testing different compounds according to the *ClinicalTrials.govClinicalTrials.gov* database.

Status	Number of clinical trials
Completed	930
Active[a]	590
Terminated	120
Total	1640

[a] Open studies: recruiting + active: not recruiting NIH, as of December 2015.

1 genes) that presents tauopathy, neurodegeneration and cognitive deficits (Cohen et al., 2013) significantly advanced the field, holding promise for use in preclinical studies. However, it is important to take into consideration that the vast majority of AD cases are sporadic with poorly understood etiology and that the most frequently used transgenic AD rodent models carry mutations that are associated with early-onset familial forms of human AD, which only account for <5% of disease cases (Selkoe, 2011).

In addition to multiple genetic mouse models and a genetic rat model (Cohen et al., 2013), several other animal models of AD have been developed including rabbits (Roher et al., 2000) and dogs (Studzinski et al., 2005). These non-transgenic models have provided additional relevant information on the physiopathology of AD (reviewed in Sarasa and Pesini, 2009). Nonetheless, it is important to keep in mind that AD mainly involves impairment in higher cognitive functions, which are hard to investigate in detail in the models described above. In order to understand higher cognitive functions in the human brain and how the brain dysfunction develops in AD, experimental animals that are more similar to humans are essential. One way to overcome this critical hurdle is to generate viable models of AD in non-human primates (NHPs). Because human and NHP brains share considerable similarities in terms of overall architecture and organization of functional networks, this strategy has the potential to greatly advance our understanding of mechanisms centrally implicated in AD pathogenesis and effective therapeutic development. It is important to note that NHPs can be trained to perform many of the perceptual and cognitive tasks that are used in behavioral and electrophysiological studies in human clinical studies. Some elegant studies evaluating cognition in NHPs relevant to aging have been carried out. For example, Nagahara et al. (2009) demonstrated that BDNF reverses neuronal atrophy and ameliorates age-related cognitive impairment in aged NHPs and Hara et al. (2014) recently showed that estrogen improved working memory in aged NHPs. However, since AD and other dementias are not a part of normal aging, it is important to gather efforts to develop a NHP model of AD.

Some studies have made use of NHPs to follow AD pathology, relying upon naturally occurring amyloid-β deposits in aged NHPs (Cai et al., 2010; Oikawa et al., 2010; Podlisny et al., 1991), a very interesting approach that may, however, take decades to come to fruition due to long lifespans. Therapeutic bispecific antibodies were recently described to cross the blood–brain barrier and to decrease Aβ levels in the brains of NHPs (Yu et al., 2014). Other groups aiming to develop an NHP AD model have carried out intracerebral injections of fibrillar Aβ into aged monkeys. This approach led to abnormal tau phosphorylation and neuronal death, but no neurofibrillary tangles were observed in this model (Geula et al., 1998; Leung et al., 2011). In fact, even aged primates are also resistant to the development of neurofibrillary tangle pathology (Heuer et al., 2012; Oikawa et al., 2010), one of the defining lesions of AD.

Recent research on the molecular mechanisms of AD pathology have evolved to include smaller aggregates of Aβ, soluble Aβ oligomers, as key neurotoxins in AD (Hardy and Selkoe, 2002) and in fact many researchers have demonstrated that oligomers are more toxic than fibrils (Ferreira and Klein, 2011; Selkoe, 2011; Viola and Klein, 2015). To take advantage of this shift in the paradigm, we conducted a novel study to test the effects of Aβ oligomers in the NHP brain by injecting Aβ oligomers into the lateral ventricle of adult cynomolgus monkeys (Forny-Germano et al., 2014). Surprisingly, neurofibrillary tangle pathology was observed shortly after the NHP brain was exposed to Aβ oligomers. When a similar protocol was used in rats, tau phosphorylation increased, but tangle pathology was not detected (Forny-Germano et al., 2014). We note that although oligomers produced pathology similar to AD, the pathology observed has been induced acutely, whereas AD progresses over decades and its clinical manifestation occurs in aging. In addition, the use of NHPs is extremely limited for most laboratories because of high price, restricted availability, maintenance requirements and ethical considerations. Nevertheless, this new NHP model offers the novel opportunity to evaluate if Aβ oligomers can lead to specific abnormalities of cognitive function in NHPs that mimic deficits observed in AD patients performing the same tasks.

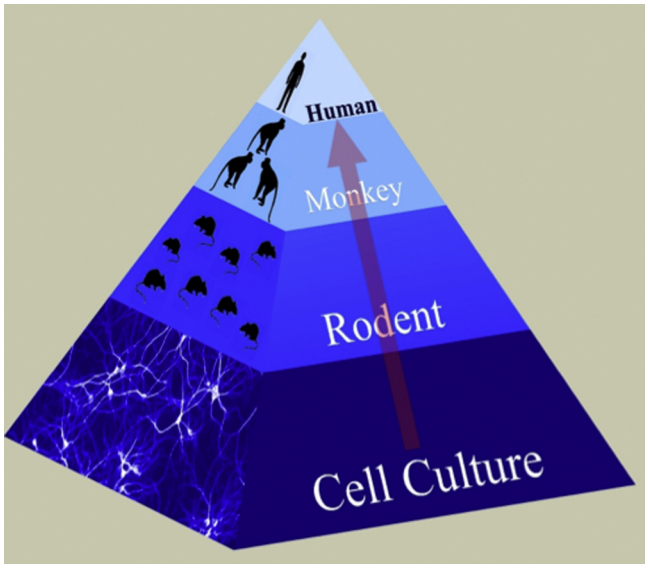

Fig. 1. Proposed multi-disciplinary strategy to investigate Alzheimer's disease (AD) mechanisms. Cell culture experiments can be used to elucidate cellular mechanisms of disease. Hypotheses related to disease mechanisms can be tested in AD transgenic rodent models and other animal models of AD. A key stage consists of extending the studies to non-human primate (NHP) models of AD. Combined efforts with different experimental models of AD will provide information on how the human disease condition develops in the human brain.

A multi-disciplinary strategy of investigating disease mechanisms from cell culture, through animal models including validated NHP models to human clinical testing is required (Fig. 1). Cell culture experiments can be used to establish basic cellular mechanisms of disease pathology. Based on information obtained in vitro, hypotheses related to disease mechanisms can be tested in AD transgenic rodent models (Oddo et al., 2003; Cohen et al., 2013) and other animal models of AD that have been developed, including rabbits (Roher et al., 2000) and dogs (Studzinski et al., 2005). A key stage then consists of extending the studies of rodents and other animals to NHP models of AD, which share many homologies with the human brain. Because of the limitations for use of primates described above, it is important to take advantage to the available models for extensive behavioral and molecular testing and then prune the protocols as one moves to the NHP model. The final critical next step will be to combine behavioral data obtained from NHPs that model AD, normal elderly individuals, and AD patients to establish clinical validity of the NHP models. Combined efforts with different animal models of AD will definitively provide important clues on how the human disease condition develops in the brain.

Development of a successful pharmacological strategy to prevent or treat AD will depend on detailed knowledge of clinically-relevant mechanisms identified to be central to the disease process and establishing a behavioral model of AD in NHPs will be a key step to reach this goal. Future treatments will likely comprise combinations of drug therapies to slow down or block pathological mechanisms, together with biologic implants and brain stimulation in targeted brain areas and circuits to promote neurogenesis, synaptogenesis and synaptic plasticity in order to restore and optimize neural networks to improve cognitive outcomes. To realize the potential of these latter approaches it will be critical to have viable NHP models of AD. This will likely be the most powerful way to improve the ability to translate basic science into clinical applications, allowing the development of safe and effective disease-modifying interventions for AD with the highest and fastest probability for success.

Acknowledgments

Research in the authors' laboratories are supported by grants from National Institute for Translational Neuroscience (INNT/Brazil) (to FGF), the Brazilian funding agencies Conselho Nacional de DesenvolvimentoCientífico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) (to FGF), Canadian Institutes for Health Research (CIHR operating grant MOP-38854 to DPM and FGF) and Canada Research Chair Program (to DPM).

References

Cai, Y., Xiong, K., Zhang, X.M., Cai, H., Luo, X.G., Feng, J.C., Clough, R.W., Struble, R.G., Patrylo, P.R., Chu, Y., Kordower, J.H., Yan, X.X., 2010. beta-Secretase-1 elevation in aged monkey and Alzheimer's disease human cerebral cortex occurs around the vasculature in partnership with multisystem axon terminal pathogenesis and beta-amyloid accumulation. Eur. J. Neurosci. 32, 1223–1238.

Cohen, R.M., Rezai-Zadeh, K., Weitz, T.M., Rentsendorj, A., Gate, D., Spivak, I., Bholat, Y., Vasilevko, V., Glabe, C.G., Breunig, J.J., Rakic, P., Davtyan, H., Agadjanyan, M.G., Kepe, V., Barrio, J.R., Bannykh, S., Szekely, C.A., Pechnick, R.N., Town, T., 2013. A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric abeta, and frank neuronal loss. J. Neurosci. 33, 6245–6256.

Cummings, J.L., Morstorf, T., Zhong, K., 2014. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Res. Ther. 6, 37.

Ferreira, S.T., Klein, W.L., 2011. The Abeta oligomer hypothesis for synapse failure and memory loss in Alzheimer's disease. Neurobiol. Learn. Mem. 96, 529–543.

Forny-Germano, L., Lyra e Silva, N.M., Batista, A.F., Brito-Moreira, J., Gralle, M., Boehnke, S.E., Coe, B.C., Lablans, A., Marques, S.A., Martinez, A.M., Klein, W.L., Houzel, J.C., Ferreira, S.T., Munoz, D.P., De Felice, F.G., 2014. Alzheimer's disease-like pathology induced by amyloid-beta oligomers in nonhuman primates. J. Neurosci. 34, 13629–13643.

Geula, C., Wu, C.K., Saroff, D., Lorenzo, A., Yuan, M., Yankner, B.A., 1998. Aging renders the brain vulnerable to amyloid beta-protein neurotoxicity. Nat. Med. 4, 827–831.

Goedert, M., Spillantini, M.G., 2006. A century of Alzheimer's disease. Science 314, 777–781.

Gotz, J., Ittner, L.M., 2008. Animal models of Alzheimer's disease and frontotemporal dementia. Nat. Rev. Neurosci. 9, 532–544.

Hara, Y., Yuk, F., Puri, R., Janssen, W.G., Rapp, P.R., Morrison, J.H., 2014. Presynaptic mitochondrial morphology in monkey prefrontal cortex correlates with working memory and is improved with estrogen treatment. Proc. Nat. Acad. Sci. U. S. A. 111 (1), 486–491.

Hardy, J., Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297, 353–356.

Heuer, E., Rosen, R.F., Cintron, A., Walker, L.C., 2012. Nonhuman primate models of Alzheimer-like cerebral proteopathy. Curr. Pharm. Des. 18, 1159–1169.

Klyubin, I., Walsh, D.M., Lemere, C.A., Cullen, W.K., Shankar, G.M., Betts, V., Spooner, E.T., Jiang, L., Anwyl, R., Selkoe, D.J., Rowan, M.J., 2005. Amyloid beta protein immunotherapy neutralizes Abeta oligomers that disrupt synaptic plasticity in vivo. Nat. Med. 11, 556–561.

LaFerla, F.M., Green, K.N., 2012. Animal models of Alzheimer disease. Cold Spring Harb. Perspect. Med. 2.

LaFerla, F.M., Oddo, S., 2005. Alzheimer's disease: Abeta, tau and synaptic dysfunction. Trends Mol. Med. 11, 170–176.

Leung, E., Guo, L., Bu, J., Maloof, M., El Khoury, J., Geula, C., 2011. Microglia activation mediates fibrillar amyloid-beta toxicity in the aged primate cortex. Neurobiol. Aging 32, 387–397.

Nagahara, A.H., Merrill, D.A., Coppola, G., Tsukada, S., Schroeder, B.E., Shaked, G.M., Wang, L., Blesch, A., Kim, A., Conner, J.M., Rockenstein, E., Chao, M.V., Koo, E.H., Geschwind, D., Masliah, E., Chiba, A.A., Tuszynski, M.H., 2009. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nat. Med. 15, 331–337.

Oddo, S., Caccamo, A., Shepherd, J.D., Murphy, M.P., Golde, T.E., Kayed, R., Metherate, R., Mattson, M.P., Akbari, Y., LaFerla, F.M., 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 39, 409–421.

Oikawa, N., Kimura, N., Yanagisawa, K., 2010. Alzheimer-type tau pathology in advanced aged nonhuman primate brains harboring substantial amyloid deposition. Brain Res. 1315, 137–149.

Podlisny, M.B., Tolan, D.R., Selkoe, D.J., 1991. Homology of the amyloid beta protein precursor in monkey and human supports a primate model for beta amyloidosis in Alzheimer's disease. Am. J. Pathol. 138, 1423–1435.

Quinn, J.F., Raman, R., Thomas, R.G., Yurko-Mauro, K., Nelson, E.B., Van Dyck, C., Galvin, J.E., Emond, J., Jack Jr., C.R., Weiner, M., Shinto, L., Aisen, P.S., 2010. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 304, 1903–1911.

Relkin, N.R., Szabo, P., Adamiak, B., Burgut, T., Monthe, C., Lent, R.W., Younkin, S., Younkin, L., Schiff, R., Weksler, M.E., 2009. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol. Aging 30, 1728–1736.

Roher, A.E., Kuo, Y.M., Potter, P.E., Emmerling, M.R., Durham, R.A., Walker, D.G., Sue, L.I., Honer, W.G., Beach, T.G., 2000. Cortical cholinergic denervation elicits vascular Abeta deposition. Ann. N. Y. Acad. Sci. 903, 366–373.

Sarasa, M., Pesini, P., 2009. Natural non-trasgenic animal models for research in Alzheimer's disease. Curr. Alzheimer Res. 6 (2), 171–178.

Selkoe, D.J., 2011. Resolving controversies on the path to Alzheimer's therapeutics. Nat. Med. 17, 1060–1065.

Studzinski, C.M., Araujo, J.A., Milgram, N.W., 2005. The canine model of human cognitive aging and dementia: pharmacological validity of the model for assessment of human cognitive-enhancing drugs. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 489–498.

Viola, K.L., Klein, W.L., 2015. Amyloid beta oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis. Acta Neuropathol. 129, 183–206.

Yoshiyama, Y., Higuchi, M., Zhang, B., Huang, S.M., Iwata, N., Saido, T.C., Maeda, J., Suhara, T., Trojanowski, J.Q., Lee, V.M., 2007. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. Neuron 53, 337–351.

Yu, Y.J., Atwal, J.K., Zhang, Y., Tong, R.K., Wildsmith, K.R., Tan, C., Bien-Ly, N., Hersom, M., Maloney, J.A., Meilandt, W.J., Bumbaca, D., Gadkar, K., Hoyte, K., Luk, W., Lu, Y., Ernst, J.A., Scearce-Levie, K., Couch, J.A., Dennis, M.S., Watts, R.J., 2014. Therapeutic bispecific antibodies cross the blood-brain barrier in nonhuman primates. Sci. Transl. Med. 6, 261ra154.