ISSN : 2350-0743

www.ijramr.com

International Journal of Recent Advances in Multidisciplinary Research
Vol. 04, Issue 03, pp.2403-2406, March, 2017

RESEARCH ARTICLE

COULD ALZHEIMER, AND RELATED DISEASES, BE DUE TO A CELLULAR REPAIR RESPONSE GONE ASTRAY?

***Jacob Z. Dalgaard**

Warwick Medical School, University of Warwick, Gibbet Hill Campus, CV47AL Coventry, United Kingdom

ARTICLE INFO

Article History:
Received 14th December, 2016
Received in revised form
25th January, 2017
Accepted 24th February, 2017
Published online 31st March, 2017

Keywords:

Tau, Alzheimer,
Dementia,
Tauopathies,
Microtubule,
Axon repair Pathway.

ABSTRACT

Dementia including Alzheimer is becoming a more significant problem in our society, which an increasing life expectancy; currently about 10% of the population develop some form of dementia during their lifetime. One form of dementia is Alzheimer that account for 50%-70% of the patients, which is characterized by the appearance of plaques and tangles in the brain that involves the aggregation of a protein named tau. Here, I propose that while tau indeed might be the underlying cause of Alzheimer, its initial aggregation could be a cellular repair-response to shearing of neuronal axons and that Alzheimer, and related tauopathies, are more likely due to inadequate removal of the aggregated protein.

INTRODUCTION

Neurons are very specialized cells with long thin appendages called axons protruding from them. The axons are protected by myelin-sheets formed within associated oligodendrocytes. These long axons, that act to replay information between nerve cells, are stabilized by both microtubule and actin fibers within them. These fibers also play an important role in the cellular transport back and forth between the end of the axon (the end of the neuronal axon interacts with another neuron's axon in what is called a synapse) and the central cellular cytoplasmand nucleus. However, the actin and microtubule fibers may potentially make the axons prone to shearing and prevent theshearing associated "axon repair". Such shearing is likely tobe caused by trauma, infection, immune cell response and mobility due to infections or micro-vascular damage (the latter observed associated with diabetes), and could be the cause of some types of dementia including Alzheimer disease. Interestingly, the protein tau, which aggregation is thought to be the underlying cause of Alzheimer and related diseases (called tauopathies) (Bancher et al., 1989; Lee et al., 2001); tau possesses several microtubule binding domains and has been shown to have a microtubule stabilizing role through it's binding (Weingarten et al., 1975; Goedert et al., 2006). It is the hyper-phosphorylation of tau, followed by it's disassociation and aggregation that is the cause of the neurological dysfunction observed for these diseases (Kopke et al., 1993; Alonso et al., 2016).

****Corresponding author: Jacob Z. Dalgaard,***
Warwick Medical School, University of Warwick, Gibbet Hill Campus, CV47AL Coventry, United Kingdom.

However, while the underlying cause of these diseases indeed is likely to beTau aggregation (Lee et al., 2001; Alonso et al., 2016), the initial cellular response involving Tau hyper-phosphorylation and aggregation, may be acellular response needed topromote axon repair. When axons are sheared or damaged, the reorganization of microtubule must be crucial, to 1) allow realignment and association of the proteinous actin and microtubule bundles, as well asfor, 2) the healing of the membranes and associated myelin sheets of the oligodendritic cells. The initial tau hyper-phosphorylation, mediated by inter-cellular kinases (Buee et al., 2010), could take placeto ensure this occurs. The hyper-phosphorylation has been shown to cause the dissociation of Tau from microtubule, as it lowers Tau's affinity for mircotubule (Alonso et al., 1994; Iqbal et al., 1994). The disassociation of Tau is likelyto increase the instability of microtubule and allows the bundles to dissociate (involving depolymerization) and reform (involving polymerization) in a more dynamic manner (Alonso et al., 1997). Furthermore, the hyper-phosphorylation also cause Tau aggregation (Alonso et al., 2006), which could have a several additional functions: 1) The aggregation could act to lower the concentration of free un-bound hyper-phosphorylated Tau, thus, further preventing it's binding to and stabilization of microtubule (Alonso et al., 1996; Alonso et al., 1997; Lee et al., 2001) It could act to amplify the speed of the removal of Tau, as hyper-phosphorylated Tau also aggregates with Tau phosphorylated at normal levels (Alonso et al., 1996; Weingarten et al., 1975) Aggregation of Tau could have a gelatinous effect on the plasma present in the axon (similar to blood clotting), potential preventing loss of factors due to

membrane damage/perforation. Furthermore, hyper-phosphorylated Tau has shown to be able to spread between neighboring cells (Saper et al., 1987; Su et al., 1997). This Tau transfer or spreadingcould act as intercellular signaling to allow neural cell and axon movement during cell divisions, immune response and cellular/axon repair.This potential function of tau, in a cellular repair response, could explain why so many different and diverse types of brain damage result in an increased long-term risk of developing Alzheimer and other tauopathies.If this model is correct, dementia associated with these tauopathies is not caused by the initial Tau aggregation per se, but an inability to reset the Tau-mediated response and remove/degrade the hyper-phosphorylated aggregated Tau. Indeed, there are several observations that seem to support this notion: 1) Two genes associated with increased susceptibility to Alzheimer, A2M (Blacker et al., 1998) and the familiar-early-onset-of-Alzheimer gene AD1 (Lawrence et al., 1992), encode proteins with proteinase inhibitorydomains (Mantuano et al., 2008; Ponte et al., 1988; Tanzi et al., 1988; Kitaguchi et al., 1988). Also, a coding single-nucleotide polymorphism (SNP) in the AD1 gene has a protective effect against Alzheimer disease (Jonsson et al., 2012).

Other Alzheimer susceptibility genes include, but are not limited to, CR1 (Smith et al., 2002), PVRL2 (Bottino et al., 2003) and MPO (Goedken et al., 2007) involved in immune-responses, UPA involved in cell migration (Kiian et al., 2003), Bin1 involved in cell cycle regulation (Sakamuro et al., 1996), PICALM involved in cellular trafficking, regulation of endocytosis, and clathrin-mediated vesicle formation (Stern et al., 2014) and finally eNOS involved in NO synthesis (Nisoli et al., 2005; Lee et al., 2001) Mutations in presenilin, a leading genetic cause of Alzheimer, cause autophagy and lysosomal pathologies (affecting protein degradation), which can be reversed by cAMP-induced lysozyme re-acidification (Coffey et al., 2014; Lokireddy et al., 2015; Rahman et al., 2016; Myeku et al., 2016; Weingarten et al., 1975) During trauma Tau hyper-phosphorylation and aggregations was found predominantly with areas critical for cognitive function and associated with hypo-metabolic rates (Ossenkoppele et al., 2016). High cellular metabolic rates as well as starvation might increase the turnover of damaged and aggregated proteins by proteases, and could explain why cognitive usage and exercise reduces the risk of Alzheimer.

Interestingly, nerve cell regeneration is observed during low calorie intake (Plunet et al., 2008; Hornsby et al., 2016; Park et al., 2013; Kalsi, 2015; Maalouf et al., 2009; Lee, 2013; Mattson et al., 2001), and interestingly, eNOS, mentioned above as an Alzheimer susceptibility gene, is induced during such calorie restriction (Nisoli et al., 2005). Indeed, during evolution central nervous system damage/injury would have correlate with low-calorie intake and starvation, which promotes intra-cellular autophagy including protein degradation. Thus, potentially a low-calorie/protein diet could potentially help promote or induce the inter-cellular removal of hyper-phosphorylated Tau aggregates, and thus, help prevent tauopathies (Halagappa et al., 2007; Schroeder et al., 2010).

REFERENCES

Alonso, A.D, Grundke-Iqbal, I., Barra, H.S., Iqbal, K. 1997. Abnormal phosphorylation of tau and the mechanism of Alzheimer neurofibrillary degeneration: Sequestration of microtubule-associated proteins 1 and 2 and the disassembly of microtubules by the abnormal tau. Proc. Natl. Acad. Sci. USA 94:298-303.

Alonso, A.D, Grundke-Iqbal, I., Iqbal, K. 1996. Alzheimer's disease hyper-phosphorylated tau sequesters normal tau into tangles of filaments and dis-assemblesmicro-tubule. Nat. Med. 2:783-787.

Alonso, A.D., Beharry, C., Corbo, C.P., Cohen, L.S. 2016. Molecular mechanism of prion-like tau-induced neurodegeneration. Alzheimer's Dementia. 1-8.

Alonso, A.D., Grundke-Iqbal, I., Barra, H.S., Iqbal, K. 1997. Abnormal phosphorylation of tau ad the mechanism of Alzheimer neurofibrillary degeneration: sequestration of microtubule-associated proteins 1 and 2 and the disassembly of microtubules by the abnormal tau. Proc. Natl. Acad. Sci. USA: 298-303.

Alonso, A.D., Li, B., Grundke-Iqbal, I., Iqbal, K. 2006. Polymerization of hyper-phosphorylated tau into filaments eliminates its inhibitory activity. Proc. Natl. Aca. Sci. USA 103:8864-8869.

Alonso, A.D., Zaidi, T., Grundke-Iqbal, I., Iqbal, K. 1994. Role of abnormally phosphorylated tau in the breakdown of microtubules in Alzheimer disease. Proc. Natl. Acad. Sci. USA 91: 5562-5566.

Bancher, C., Brunner, C., Lassmann, H., Budka, H., Jellinger, K., Wicje, G., et al. 1989. Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. Brain Res. 477:90-99.

Blacker, D., Wilcox, M.A., Laird, N.M., Rodes, L., Horvath, S.M., Go, R.C., Perry, R., Watson, B. Jr., Bassett, S.S., McInnis, M.G., Albert, M.S., Hyman, B.T., Tanzi, R.E. 1998. Alpha-2 macroglobulin is genetically associated with Alzheimer disease. Nat. Genet.19:357-360.

Bottino, C., Castriconi, R., Pende, D., Rivera, P., Nanni, M., Carnemolla, B., Cantoni, C., Grassi, J., Marcenaro, S., Reymond, N., Vitale, M., Moretta, L., Lopez, M., Moretta, A. 2003. Identification of PVR (CD155) and nectin-2 (CD112) as cell surface ligands for the human DNAM-1 (CD226) activating molecule. J. Exp. Med. 198: 557-567, 2003.

BueeL., Troquier, L., Burnouf, S., Belarbi, K., Van der Jeugd, A., Ahmed, T., et al. 2010. From Tau phosphorylation to tau aggregation: what about neuronal death? Biochem. Soc. Trans. 38: 967-972.

Coffey E.E., Beckel, J.M. Laties, A.M. and Mitchell, C.H. 2014. Lysomomal alkalization and dysfunction in human fibroblasts with the Alzheimer's disease-linked presenilin 1 A246E mutation can be reversed with cAMP. Neuroscience 263:111-124.

Goedert, M., Klug, A., Crowther R.A. 2006. Tau protein, the paired helical filament and Alzheimer's disease. J. Alzheimers Dis. 9: 195-207.

Goedken, M., McCormick, S., Leidal, K. G., Suzuki, K., Kameoka, Y., Astern, J. M., Huang, M., Cherkasov, A., Nauseef, W. M. 2007. Impact of two novel mutations on the structure and function of human myeloperoxidase. J. Biol. Chem. 282: 27994-28003.

Halagappa, V.K., Guo, Z., Pearson, M., Matsuoka, Y., Cutler, R.G., Laferla, F.M., Mattson, M.P. 2007. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease.Neurobiol. Dis. 26:212-220.

Hornsby, A.K., Redhead, Y.T., Rees, D.J., Ratcliff, M.S.,Reichenbach, A., Wells, T., Francis, L., Amstalden, K., Andrews, Z.B., Davies, J.S. 2016. Short-term calorie restriction enhances adult hippocampal neurogenesis and remote fear memory in a Ghsr-dependent manner. Psychoneuroendocrinology.63:198-207.

Iqbal, K., Zaidi, T., Bancher, C., Grundke-Iqbal, K., 1994. Alzheimer paired helical filaments. Restoration of the biological activity by dephosphorylation. FEBS Lett. 349: 104-108.

Jonsson, T., Atwal, J.K., Steinberg, S., Snaedal, J., Jonsson, P.V., Bjornsson, S., Stefansson, H., Sulem, P., Gudbjartsson, D., Maloney, J., Hoyte, K., Gustafson, A., et al. 2012. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488: 96-99.

Kalsi, D.S. 2015. What is the effect of fasting on the lifespan of neurons?Ageing. Res. Rev. 24:160-165.

Kiian, I., Tkachuk, N., Haller, H., Dumler, I. 2003. Urokinase-induced migration of human vascular smooth muscle cells requires coupling of the small GTPaseRhoA and Rac1 to the Tyk2/PI3-K signalling pathway. Thromb. Haemost. 89: 904-914.

Kitaguchi, N., Takahashi, Y., Tokushima, Y., Shiojiri, S., Ito, H. 1988. Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity. Nature 331: 530-532.

Kopke, E., Tung, Y.C. Shaike, S., Alonso, A.D., Iqbal, K., Grundke-Igbal, I. 1993. Microtubule-associated protein Tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. J. Biol. Chem. 268: 24374-24384.

Lawrence, S., Keats, B.J., Morton, N.E. 1992. The AD1 locus in familial Alzheimer disease. Ann. Hum. Genet. 56:295-301.

Lee, S., Notterpek, L. 2013. Dietary restriction supports peripheral nerve health by enhancing endogenous protein quality control mechanisms. ExpGerontol. 48:1085-1090.

Lee, V.M., Goedert M., Trojanowski, J.Q. 2001. Neurodegenerative tauopathies. Annu. Rev. Neurosci. 24:121-59.

Lokireddy, S., Kukushkin, N.V., Goldberg, A.L. 2015. cAMP-induced phosphorylation of 26S proteasomes on Rpn6/PSMD11 enhances their activity and the degradation of misfolded proteins. Proc. Natl. Acad. Sci. U S A. 112:E7176-185.

Maalouf, M., Rho, J.M., Mattson, M.P. 2009. Theneuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res. Rev. 59:293-315.

Mantuano, E., Mukandala, G., Li, X., Campana, W.M., Gonias, S.L. 2008. Molecular dissection of the human alpha2-macroglobulin subunit reveals domains with antagonistic activities in cell signaling. J. Biol. Chem.283:19904-19911.

Mattson, M.P., Duan, W., Lee, J., Guo, Z. 2001. Suppression of brain aging and neurodegenerative disorders by dietary restriction and environmental enrichment: molecular mechanisms. Mech. Ageing Dev. 122:757-78.

Myeku, N., Clelland, C.L., Emrani, S., Kukushkin, N.V., Yu, W.H., Goldberg, A.L., Duff, K.E. 2016. Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. Nat. Med. 22:46-53.

Nisoli, E., Tonello, C., Cardile, A., Cozzi, V., Bracale, R., Tedesco, L., Falcone, S., Valerio, A., Cantoni, O., Clementi, E., Moncada, S., Carruba, M.O. 2005. Calorie restriction promotes mitochondrial biogenesis by inducing the expression ofeNOS. Science 310: 314-317.

Ossenkoppele, R., Schonhaut, D.R., Schöll, M., Lockhart, S.N., Ayakta, N., Baker, S.L., O'Neil, J.P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z.A., Bettcher, B.M., Vossel, K.A., Kramer, J.H., Gorno-Tempini, M.L., Miller, B.L., Jagust, W.J., Rabinovici, G.D. 2016. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139:1551-1567.

Park, J.H., Glass, Z., Sayed, K., Michurina, T.V., Lazutkin, A., Mineyeva, O., Velmeshev, D., Ward, W.F., Richardson, A., Enikolopov, G. 2013. Calorie restriction alleviates the age-related decrease in neural progenitor cell division in the aging brain. Eur. J. Neurosci. 37:1987-1993.

Plunet, W.T., Streijger, F., Lam, C.K., Lee, J.H., Liu, J., Tetzlaff, W.2008. Dietary restriction started after spinal cord injury improves functional recovery. Exp. Neurol. 213:28-35.

Ponte, P., Gonzalez-DeWhitt, P., Schilling, J., Miller, J., Hsu, D., Greenburg, B., Davis, K., Wallace, W., Lieberburg, I., Fuller, F., Cordell, B. 1988. A new A4 amyloid mRNA contains a domain homologous to serine proteinase inhibitors. Nature 331: 525-527.

Rahman, N., Ramos-Espiritu, L., Milner, T.A., Buck, J., Levin L.R. 2016. Soluble adenylyl cyclase is essential for proper lysosomal acidification. J. Gen. Physiol. 148:325-339.

Sakamuro, D., Elliott, K. J., Wechsler-Reya, R., Prendergast, G. C. 1996. BIN1 is a novel MYC-interacting protein with features of a tumour suppressor. Nature Genet. 14: 69-77.

Saper, C.B., Wainer, B.H., German, D.C. 1987. Axonal and transneuronal transport in the transmission of neurological disease: potential role in system degenerations, including Alzheimer's disease. Neuroscience 23: 389-398.

Schroeder JE, Richardson JC, Virley DJ. 2010. Dietary manipulation and caloric restriction in the development of mouse models relevant to neurological diseases.Biochim. Biophys. Acta. 1802:840-846.

Smith, B.O., Mallin, R.L., Krych-Goldberg, M., Wang, X., Hauhart, R.E., Bromek, K., Uhrin, D., Atkinson, J.P., Barlow, P.N. 2002. Structure of the C3b binding site of CR1 (CD35), the immune adherence receptor. Cell 108: 769-780.

Stern, J.A., White, S.N., Lehmkuhl, L.B., Reina-Doreste, Y., Ferguson, J.L., Nascone-Yoder, N.M., Meurs, K. M. 2014. A single codon insertion in PICALM is associated with development of familial subvalvular aortic stenosis in Newfoundland dogs. Hum. Genet. 133: 1139-1148.

Su, J.H., Deng, G., Cotman, C.W. 1997. Transneuronal degeneration in the spread of Alzheimer's disease pathology: immunohistochemical evidence for the transmission of tau hyperphosphorylation. Neurobiol. Dis. 4:365-367.

Tanzi, R.E., McClatchey, A.I., Lamperti, E.D., Villa-Komaroff, L., Gusella, J.F., Neve, R.L. 1988. Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease. Nature 331: 528-530.

Weingarten, M.D., Lockwood, A.H., Hwo, S.Y., Kirschner, M.W. 1975. A protein factor essential for microtubule assembly. Proc. Natl. Acad. Sci. USA. 72: 1858-62.

****