Name of Disorder:
Alzheimer's disease

Essay Title:
Alzheimer's disease, it's time for a cure

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Date:
28th June, 2013

Alzheimer's disease; its time for a cure

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder symptomatically characterised by impaired memory and alterations to personality. Unfortunately, little is known about the causes of AD, early detection is limited, and there is currently no cure. Slowing the rate of progression of AD and enhancing the brains own ability to regenerate are current key focal points in establishing a treatment for AD. However, there is still a vast amount unknown about this complex disorder and further investigation into normal and diseased brain function is essential.

Pathologically, AD is characterised by the abnormal cleaving of the amyloid precursor protein (APP) resulting in amyloid beta (Aβ) deposition. In the normal state, cleavage of APP results in a 40 amino acid fragment termed $A\beta_{40}$. However, in AD, APP is often cleaved into the 42 amino acid fragment ($A\beta_{42}$), which is more fibrillogenic. This fibrillogenic form is often what results in the formation of plaques within the cortex, hippocampus and amygdala. These areas are involved in memory, learning and higher thinking. As a result of degeneration in these areas, patients exhibit cognitive dysfunction.

Aβ deposition and the subsequent plaque load have gained enormous attention as both a hallmark and a therapeutic target for AD. As such, many developed therapies have been based around preventing the production of, or increasing the clearance of, the Aβ peptide (Liu B *et al*, 2013; Demattos RB *et al*, 2012; Liu YH *et al*, 2012). However, to date, therapies targeted at reducing Ab have disappointingly had little success in clinical trials (Liu B *et al*, 2013; Demattos RB *et al*, 2012; Liu YH *et al*, 2012). This is potentially due to therapies being delivered too late in the disease progression, though this may also give indication that Aβ is not a central component of the disorder. Despite this, intense debate amongst the scientific community remains as to the clinical relevance of Aβ as both a cause and a hallmark of AD. This is because there is often little correlation between plaque deposition and cognitive status.

Whilst the hallmarks of AD include plaque deposition, other cellular processes also occur. Numerous mouse model studies have shown that cell loss and inflammatory processes occur well before plaque formation and cognitive dysfunction (Wright *et al*, 2013). Additionally, analysis of human brain tissue from AD patients and studies conducted in pre-clinical animal models of AD indicate that disease onset may also be associated with inhibition of neurogenesis (Mu Y and Gage FH, 2011; Rodrigues JJ *et al,* 2008; Li B *et al*, 2008). Neurogenesis is the process by which new neurons are formed from populations of stem cells in the adult brain. It has been shown that neurogenesis is critical to brain function playing an important role in memory and learning (Geihig CS *et al*, 2012; Blaiss CA *et al*, 2011; Ohira K *et al*, 2010; Cho KO *et al*, 2010; Sun D *et al*, 2007; Bonfanti L *et al*, 2011). Therefore, agents or approaches that stimulate neurogenesis in the adult brain could be therapeutically significant in Alzheimer's disease.

With the predicted exponential growth rate of AD worldwide, there is now an eager need for a deeper understanding of AD pathology. A marker for early detection is essential, and treatment options are critically required. It is plausible that memory loss and other clinical signs of AD are late stage events,

occurring well after the development of neuroinflammation and neuronal cell loss. Therefore, regardless of the ultimate therapeutic approach it is reasoned that therapies will certainly need to be started early in the disease cascade. We are now at a stage where there is a pressing need to identify early markers and create treatments for individuals living with AD that are viable and target specific. Further research into early biomarkers and cell signaling dysfunction are crucial to understand this devastating disorder.

References:

1. Liu B, Frost JL, Sun J, Fu H, Grimes S, Blackburn P, Lemere CA. MER5101, a novel Aβ1-15:DT conjugate vaccine, generates a robust anti-Aβ antibody response and attenuates Aβ pathology and cognitive deficits in APPswe/PS1ΔE9 transgenic mice. J Neurosci. 2013 Apr 17;33(16):7027-37.
2. Demattos RB, Lu J, Tang Y, Racke MM, Delong CA, Tzaferis JA, Hole JT, Forster BM, McDonnell PC, Liu F, Kinley RD, Jordan WH, Hutton ML. A plaque-specific antibody clears existing β-amyloid plaques in Alzheimer's disease mice. Neuron. 2012 Dec 6;76(5):908-20.
3. Liu YH, Giunta B, Zhou HD, Tan J, Wang YJ. Immunotherapy for Alzheimer disease: the challenge of adverse effects. Nat Rev Neurol. 2012 Aug;8(8):465-9.
4. Wright AL, Zinn R, Hohensinn B, Konen LM, Beynon SB, Tan RP, Clark IA, Abdipranoto A, Vissel B. Neuroinflammation and neuronal loss precede Aβ plaque deposition in the hAPP-J20 mouse model of Alzheimer's disease. PLoS One. 2013;8(4):e59586.
5. Mu Y and Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener 2011; 6:85
6. Rodriguez JJ, Jones VC and Verkhatsky A. Impaired cell proliferation in the subventricular zone in an Alzheimer's disease model. PLoS ONE 2008; 3(8):e2935
7. Li B, Yamamori H, Tatebayashi Y et al. Failure of neuronal maturation in Alzheimer disease dentate gyrus. J Neuropathol Exp Neurol. 2008; 67(1): 78-84
8. Geibig CS, Keiner S, Redecker C. Functional recruitment of newborn hippocampal neurons after experimental stroke. Neurobiol Dis 2012; 46:431-439.
9. Blaiss CA, Yu TS, Zhang G, et al. Temporally specified genetic ablation of neurogenesis impairs cognitive recovery after traumatic brain injury. J Neurosci 2011; 31:4906-4916.
10. Ohira K, Furuta T, Hioki H, et al. Ischemia-induced neurogenesis of neocortical layer 1 progenitor cells. Nat Neurosci 2010; 13:173-179.
11. Cho KO, Kim SY. Effects of brain insults and pharmacological manipulations on the adult hippocampal neurogenesis. Arch Pharm Res 2010; 33:1475-1488.
12. Sun D, McGinn MJ, Zhou Z, et al. Anatomical integration of newly generated dentate granule neurons following traumatic brain injury in adult rats and its association to cognitive recovery. Exp Neurol 2007; 204:264-272.
13. Bonfanti L, Peretto P. Adult neurogenesis in mammals – a theme with many variations. Eur J Neurosci 2011; 34:930-950.