HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Alzheimers Dement. 2009 March ; 5(2): 143–146. doi:10.1016/j.jalz.2009.01.013.

Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." Rationale and recommendations for first evaluating anti-Alzheimer's disease medications in acute brain injury patients

James W. Simpkins[a,*], **Joshua W. Gatson**[b], and **Jane G. Wigginton**[b]

[a]Department of Pharmacology and Neuroscience, Institute for Aging and Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, TX, USA

[b]Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

1. Rationale for utilization of acute brain injury for drug screening for Alzheimer's disease

A considerable body of evidence, including dozens of failed clinical trials, argues for the need to start anti-Alzheimer's disease (AD) therapy long before clinical symptoms of the disease appear. This need for therapy that begins years, if not decades, before AD symptoms are clinically apparent would cost amounts of money far in excess of the financial risks that even large pharmaceutical companies are willing to bear for a clinical trial, and the durations of proposed trials are far in excess of the normal funding cycle of National Institutes of Health grants. Moreover, the potential risk of side effects or drug interactions from the administration of extremely long-term dosing of an unproven drug in a population that may never develop Alzheimer's disease is undesirable, and may pose an unacceptable clinical trial risk profile.

As such, few primary AD prevention trials are now ongoing, despite preclinical evidence for the efficacy of a number of potential disease-modifying drugs. The prohibitive costs of primary prevention trials for anti-AD drugs could be addressed in a number of ways. First, the use of surrogate biomarkers for disease progression was proposed [1]. This entails the identification of genetic, molecular, or biochemical markers that change in a way indicative of disease progression. Unfortunately, to date, there is no agreement on which markers to assess, either individually or collectively, for disease progression.

An alternative approach involves the assessment of potential disease-modifying drugs in conditions that share common features of AD neuropathology, but that are more acute and easily diagnosable in nature. Here we propose to use acute traumatic brain injury (TBI) and/or stroke as such conditions for the testing of drugs that may modify AD neuropathology, and therefore AD disease progression. The adoption of such an approach could allow for the identification of clinically therapeutic "hits" that would not only be of

*Corresponding author. Tel.: 817-735-0498; Fax: 817-735-2091. jsimpkin@hsc.unt.edu.

value in the treatment of acute brain injury, but, as importantly, could suggest effective therapies for more chronic brain-injury condition such as AD. These provocative clinical data might not only encourage the sponsorship of clinical trials regarding the efficacy of these drugs as anti-AD therapy, but could also simultaneously provide a revenue stream to the sponsoring company by their use in acute stroke and TBI patients. Finally, these data can be generated in a comparatively short time, given the acute nature of brain injury and the rapidity of onset of Alzheimer's-like syndrome in these patient populations.

2. Evidence for brain trauma in the risk for AD and its neuropathology

The aforementioned proposal requires the identification of acute brain injury processes that 1) are associated with an increased risk of AD, and 2) show evidence for the rapid development of AD-like neuropathology after the injury. Two such cases are TBI and stroke.

It has long been noted that many patients with traumatic brain injury subsequently develop a dementia-like neurological decline. The preponderance of recent evidence indicates that such dementia has significant AD-like qualities [2]. A retrospective meta-analysis by Fleminger et al. [3] found that, in 15 case-control studies, TBI was a significant risk factor for the development of AD in male patients (the most common victims of TBI; odds ratio, 2.29; 95% confidence interval, 1.47–2.06). In TBI patients surviving only 6–18 days after a head injury, Robert et al. [4] noted extensive deposits of beta-A amyloid (Aβ) in the cortex of 6/16 patients (median age, 46 years). In a later, larger study of 152 patients, this same group found that 20% of TBI patients in their teens to 30s (survival time, 4 hours to 5 years) had deposits in cortical areas [5]. In patients surviving 18 hours to 9 days after TBI, Smith et al. [6] noted extensive accumulations of Aβ, at autopsy, in the terminal ends of disconnected axons after brain trauma. McKenzie et al. [7] studied the brains of 55 patients who died within 24 hours of head injury, and found β-amyloid precursor protein (APP) accumulation in 71% of cases, with the earliest detectable at 2 hours of survival. Ikonomovic et al. [8] examined human temporal-cortex tissue surgically excised after severe brain injury, and found diffuse "immature-appearing" cortical Aβ deposits in one third of the patients as early as 2 hours after injury.

In previous animal studies of TBI, markers of AD such as APP, Aβ, and tau were found to increase early, and to persist long after injury. Earlier studies demonstrated a significant elevation in APP immunoreactivity within neurons [9–11]. Various models of TBI demonstrated that by 30 minutes after injury, an increase in APP levels in rats occurred. This increase in APP localized in neuronal axons within the thalamus, cortex, striatum, and hippocampus [9–14]. An increase in the neurotoxic Aβ was also reported in rats, rabbits, and pigs [9–14]. Transgenic animal models of AD were used in TBI studies to explore further the effects of Aβ deposition and plaque formation on neuronal survival and cognition. These models noted an increase in number of Aβ deposits and in neuronal cell death, resulting in significant memory impairment [15–19]. Moreover, TBI in rats induced a significant increase in expression of other markers, products, and pathways involved in AD, such as beta-secretase (BACE-1) [20] and tau. In TBI studies, cleaved and hyperphosphorylated tau increased in both wild-type and AD transgenic animals [6,21–23] and human subjects [24].

These results suggest that TBI in animals increases the risk for AD-like pathology and behavior.

There is ample evidence that after a stroke, a progressive decline in cognition occurs in human subjects and in animal models, with evidence for the rapid development of AD-like neuropathology. Tatemichi et al. [25] reported that the incidence of dementia was 6.7% among patients after 1 year of follow-up in a sample of 610 patients who were initially nondemented after a stroke. Bornstein et al. [26] reported that 32% of patients who were initially nondemented after a stroke developed dementia during 5 years of follow-up after their first ischemic stroke. Henon et al. [27] examined a cohort of 169 patients who had been nondemented before the onset of stroke, and reported that the cumulative proportion of patients with incident dementia was 21.3% after 3 years of follow-up. Altieri et al. [28] assessed 191 nondemented stroke patients for 4 years of follow-up, and found that the incidence of dementia increased gradually, with 21.5% patients developing dementia by the end of follow-up. In population-based studies of stroke and dementia, Kokmen et al. [29] reviewed the medical records of 971 patients who were free of dementia before their first stroke. The cumulative incidence of dementia was 7% at 1 year, 10% at 3 years, 15% at 5 years, and 23% at 10 years. Desmond et al. [30] performed functional assessments annually on 334 ischemic-stroke patients and 241 stroke-free control subjects, all of whom were nondemented during baseline examinations, and found a progressive course of dementia, with an incidence rate of 8.94 per 100 person-years in the stroke cohort, and 1.37 cases per 100 person-years in the control cohort. In two studies based on patients presenting with a lacunar infarction as their first stroke, Samuelsson et al. [31] found that 4.9% and 9.9% of 81 patients developed dementia after 1 and 3 years of follow-up, respectively, and Loeb et al. [32] found that 23.2%patients developed dementia during an average of 4 years of follow-up.

Animal research demonstrated that AD neuropathologies can be induced in the rat middle cerebral artery occlusion (MCAO) model, suggesting that this model may be useful as a nontransgenic model to discover potential therapeutics for AD. Alz-50-immunoreactive granules are found around cerebral infarctions after ischemic strokes in gerbil, rats, and humans [33–35]. Cerebral ischemia induces tau hyperphosphorylation [34,36–38] and an increase in BACE levels [39,40]. Ischemic stroke induces abnormal cell-cycle molecules, such as cdc2, cyclin B1, and nonmitotic cdk5 [41]. Further, increased cdk5 mRNA and protein in the human brain after acute ischemic stroke were reported [42]. Cdk5 is a key kinase in tau hyperphosphorylation and AD pathogenesis [43,44]. Ischemic injury-induced cdk5 activation is also related to another key pathological feature, amyloid plaque formation [45,46].

3. Protocol for drug assessment in acute brain injury studies

Several factors may contribute to the successful execution of acute brain injury studies. Some drugs may require extremely rapid administration after an acute brain injury to achieve maximal efficacy. Significant benefit may also accrue from prehospital administration by emergency medical services crews or immediately upon hospital arrival. In this instance, the acquisition of a Food and Drug Administration investigative new drug

approval (IND) application approval for an “exception from informed consent” trial may significantly facilitate early intervention. Performing these studies at level I and II trauma centers and primary stroke centers may also provide two important benefits: the ability to optimize study enrollment, and a general avoidance of transfer of patients to another hospital for a higher level of care. The latter helps ensure continuity and consistency of both study therapy and standard treatment, and may optimize follow-up. Finally, it is essential to have support for the clinical study from all patient-care team members involved in treatment, because these patients can have very complicated clinical courses, involving numerous disciplines of medicine. Continued access to a patient allows uninterrupted administration of study medication and follow-up, regardless of the discipline of members of the primary-care team.

4. Conclusions and recommendations

In conclusion, assessments of potential anti-AD drugs in clinical trials for the treatment of TBI and/or stroke could significantly benefit both acute and chronic brain-injured patients, while rapidly providing clinical data at a comparatively low cost for the assessment of the potential efficacy of drugs as anti-AD therapy.

To optimize this model for the assessment of potential anti-AD drugs in the acute brain injury setting, several enhancements in our approach to acute emergency medicine drug trials are needed. First, community and Food and Drug Administration awareness and education of the importance of “exception from informed consent” studies must continue, and must be enhanced to assure early drug delivery. Second, pharmaceutical companies need to embrace this approach for the initial screening of potential anti-AD drug-testing. Third, investments in clinical research infrastructures within level I and II trauma centers and primary stroke centers are necessary, to enhance their capacity to identify and treat study participants. Finally, relationships between research scientists, research physicians, and clinical faculty must be encouraged and developed, to ensure the successful conduct of drug-intervention trials via an integration of the research and treatment teams at these sites.

References

1. Aisen P, Albert M, Breitner JCS, Buckholtz N, Corey-Bloom JP, Cummings JL, et al. Preventing dementia: following in Leon Thal’s footsteps. Alzheimers Dement. 2008; 4:156–163. [PubMed: 18631960]
2. Szczygielski J, Mautes A, Steudel WI, Falkai P, Bayer TA, Wirths O. Traumatic brain injury: cause or risk of Alzheimer’s disease? A review of experimental studies. J Neural Transm. 2005; 112:1547–1564. [PubMed: 15959838]
3. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer’s disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry. 2003; 74:857–862. [PubMed: 12810767]
4. Roberts GW, Gentleman SM, Lynch A, Graham DI. Beta A4 amyloid protein deposition in brain after head trauma. Lancet. 1991; 338:1422–1423. [PubMed: 1683421]
5. Roberts GW, Gentleman SM, Lynch A, Murray L, Landon M, Graham DI. Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer’s disease. J Neurol Neurosurg Psychiatry. 1994; 57:419–425. [PubMed: 8163989]
6. Smith DH, Chen XH, Iwata A, Graham DI. Amyloid beta accumulation in axons after traumatic brain injury in humans. J Neurosurg. 2003; 98:1072–1077. [PubMed: 12744368]

7. McKenzie KJ, McLellan DR, Gentleman SM, Maxwell WL, Gennarelli TA, Graham DI. Is beta-APP a marker of axonal damage in short-surviving head injury? Acta Neuropathol (Berl). 1996; 92:608–613. [PubMed: 8960319]

8. Ikonomovic MD, Uryu K, Abrahamson EE, Ciallella JR, Trojanowski JQ, Lee VM, et al. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. Exp Neurol. 2004; 190:192–203. [PubMed: 15473992]

9. Lewen A, Li GL, Olsson Y, Hillered L. Changes in microtubule-associated protein 2 and amyloid precursor protein immunoreactivity following traumatic brain injury in rat: influence of MK-801 treatment. Brain Res. 1996; 719:161–171. [PubMed: 8782876]

10. Otsuka N, Tomonaga M, Ikeda K. Rapid appearance of beta-amyloid precursor protein immunoreactivity in damaged axons and reactive glial cells in rat brain following needle stab injury. Brain Res. 1991; 568:335–338. [PubMed: 1814579]

11. Pierce JE, Trojanowski JQ, Graham DI, Smith DH, McIntosh TK. Immunohistochemical characterization of alterations in the distribution of amyloid precursor proteins and beta-amyloid peptide after experimental brain injury in the rat. J Neurosci. 1996; 16:1083–1090. [PubMed: 8558237]

12. Albensi BC, Igoechi C, Janigro D, Ilkanich E. Why do many NMDA antagonists fail, while others are safe and effective at blocking excitotoxicity associated with dementia and acute injury? Am J Alzheimers Dis Other Dement. 2004; 19:269–274.

13. Chen XH, Siman R, Iwata A, Meaney DF, Trojanowski JQ, Smith DH. Long-term accumulation of amyloid-beta, beta-secretase, presenilin-1, and caspase-3 in damaged axons following brain trauma. Am J Pathol. 2004; 165:357–371. [PubMed: 15277212]

14. Hamberger A, Huang YL, Zhu H, et al. Redistribution of neurofilaments and accumulation of beta-amyloid protein after brain injury by rotational acceleration of the head. J Neurotrauma. 2003; 20:169–178. [PubMed: 12675970]

15. Brody DL, Holtzman DM. Morris water maze search strategy analysis in PDAPP mice before and after experimental traumatic brain injury. Exp Neurol. 2006; 197:330–340. [PubMed: 16309676]

16. Hartman RE, Laurer H, Longhi L, Bales KR, Paul SM, McIntosh TK, et al. Apolipoprotein E4 influences amyloid deposition but not cell loss after traumatic brain injury in a mouse model of Alzheimer's disease. J Neurosci. 2002; 22:10083–10087. [PubMed: 12451108]

17. Laurer HL, Bareyre FM, Lee VM, Trojanowski JQ, Longhi L, Hoover R, et al. Mild head injury increasing the brain's vulnerability to a second concussive impact. J Neurosurg. 2001; 95:859–870. [PubMed: 11702878]

18. Nakagawa Y, Nakamura M, McIntosh TK, Rodriguez A, Berlin JA, Smith DH, et al. Traumatic brain injury in young, amyloid-beta peptide overexpressing transgenic mice induces marked ipsilateral hippocampal atrophy and diminished Abeta deposition during aging. J Comp Neurol. 1999; 411:390–398. [PubMed: 10413774]

19. Nakagawa Y, Reed L, Nakamura M, McIntosh TK, Smith DH, Saatman KE, et al. Brain trauma in aged transgenic mice induces regression of established Abeta deposits. Exp Neurol. 2000; 163:244–252. [PubMed: 10785464]

20. Smith DH, Nakamura M, McIntosh TK, Trojanowski JQ, Longhi L, Hoover R, et al. Brain trauma induces massive hippocampal neuron death linked to a surge in beta-amyloid levels in mice overexpressing mutant amyloid precursor protein. Am J Pathol. 1998; 153:1005–1010. [PubMed: 9736050]

21. Blasko I, Beer R, Bigl M, Apelt J, Franz G, Rudzki D, et al. Experimental traumatic brain injury in rats stimulates the expression, production and activity of Alzheimer's disease beta-secretase (BACE-1). J Neural Transm. 2004; 111:523–536. [PubMed: 15057522]

22. Gabbita SP, Scheff SW, Menard RM, Roberts K, Fugaccia I, Zemlan FP. Cleaved-tau: a biomarker of neuronal damage after traumatic brain injury. J Neurotrauma. 2005; 22:83–94. [PubMed: 15665604]

23. Genis L, Chen Y, Shohami E, Michaelson DM. Tau hyperphosphorylation in apolipoprotein E-deficient and control mice after closed head injury. J Neurosci Res. 2000; 60:559–564. [PubMed: 10797559]

24. Irving EA, Nicoll J, Graham DI, Dewar D. Increased tau immunoreactivity in oligodendrocytes following human stroke and head injury. Neurosci Lett. 1996; 213:189–192. [PubMed: 8873146]
25. Tatemichi TK, Foulkes MA, Mohr JP, Hewitt JR, Hier DB, Price TR, et al. Dementia in stroke survivors in the Stroke Data Bank cohort. Prevalence, incidence, risk factors, and computed tomographic findings. Stroke. 1990; 21:858–866. [PubMed: 2349588]
26. Bornstein NM, Gur AY, Treves TA, Reider-Groswasser I, Aronovich BD, Klimovitzky SS, et al. Do silent brain infarctions predict the development of dementia after first ischemic stroke? Stroke. 1996; 27:904–905. [PubMed: 8623111]
27. Henon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia: incidence and relationship to prestroke cognitive decline. Neurology. 2001; 57:1216–1222. [PubMed: 11591838]
28. Altieri M, Di Piero V, Pasquini M, Gasparini M, Vanacore N, Vicenzini E, et al. Delayed poststroke dementia: a 4-year follow-up study. Neurology. 2004; 62:2193–2197. [PubMed: 15210881]
29. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960–1984). Neurology. 1996; 46:154–159. [PubMed: 8559366]
30. Desmond DW, Moroney JT, Sano M, Stern Y. Incidence of dementia after ischemic stroke: results of a longitudinal study. Stroke. 2002; 33:2254–2260. [PubMed: 12215596]
31. Samuelsson M, Soderfeldt B, Olsson GB. Functional outcome in patients with lacunar infarction. Stroke. 1996; 27:842–846. [PubMed: 8623103]
32. Loeb C, Gandolfo C, Croce R, Conti M. Dementia associated with lacunar infarction. Stroke. 1992; 23:1225–1229. [PubMed: 1519275]
33. Dewar D, Graham DI, Teasdale GM, McCulloch J. Alz-50 and ubiquitin immunoreactivity is induced by permanent focal cerebral ischaemia in the cat. Acta Neuropathol (Berl). 1993; 86:623–629. [PubMed: 8310818]
34. Wen Y, Yang S, Liu R, Simpkins JW. Transient cerebral ischemia induces site-specific hyperphosphorylation of tau protein. Brain Res. 2004; 1022:30–38. [PubMed: 15353210]
35. Ikeda K, Akiyama H, Arai T, Kondo H, Haga C, Tsuchiya K, et al. Neurons containing Alz-50-immunoreactive granules around the cerebral infarction: evidence for the lysosomal degradation of altered tau in human brain? Neurosc Lett. 2000; 284:187–189.
36. Wen Y, Yang SH, Liu R, Brun-Zinkernagel AM, Koulen P, Simpkins JW. Transient cerebral ischemia induces aberrant neuronal cell cycle reentry and Alzheimer's disease-like tauopathy in female rats. J Biol Chem. 2004; 279:22684–22692. [PubMed: 14982935]
37. Wen Y, Yang SH, Liu R, Sarkar S, Simpkins JW. Cell-cycle regulators are involved in transient cerebral ischemia induced neuronal apoptosis in female rats. FEBS Lett. 2005; 579:4591–4599. [PubMed: 16098510]
38. Wen Y, Yang SH, Liu R, Perez E, Brun-Zinkernagel AM, Koulen P, et al. Cdk5 is involved in NFT-like tauopathy induced by transient cerebral ischemia in female rats. Biochim Biophys Acta. 2007; 1772:473–483. [PubMed: 17113760]
39. Wen Y, Onyewuchi O, Yang SH, Liu R, Simpkins JW. Increased β-secretase activity and expression in rats following transient cerebral ischemia. Brain Res. 2004; 1009:1–8. [PubMed: 15120577]
40. Tesco G, Koh YH, Kang E, Cameron A, Das S, Sena-Esteves M, et al. Depletion of GGA3 stabilizes BACE and enhances β-secretase activity. Neuron. 2007; 54:721–737. [PubMed: 17553422]
41. Kesavapany S, Li BS, Amin N, Zheng YL, Grant P, Pant HC. Neuronal cyclin-dependent kinase 5: role in nervous system function and its specific inhibition by the Cdk5 inhibitory peptide. Biochim Biophys Acta. 2004; 1697:143–153. [PubMed: 15023357]
42. Mitsios N, Pennucci R, Krupinski J, Sanfeliu C, Gaffney J, Kumar P, et al. Expression of cyclin-dependent kinase 5 mRNA and protein in the human brain following acute ischemic stroke. Brain Pathol. 2007; 17:11–23. [PubMed: 17493033]
43. Cruz JC, Tsai LH. Cdk5 deregulation in the pathogenesis of Alzheimer's disease. Trends Mol Med. 2004; 10:452–458. [PubMed: 15350898]

44. Monaco EA III, Vallano ML. Role of protein kinases in neurodegenerative disease: cyclin-dependent kinases in Alzheimer's disease. Front Biosci. 2005; 10:143–159. [PubMed: 15574357]

45. Wen Y, Yu WH, Maloney B, Bailey J, Ma J, Marié I, et al. Transcriptional regulation of beta-secretase by p25/cdk5 leads to enhanced amyloidogenic processing. Neuron. 2008; 57:680–690. [PubMed: 18341989]

46. Vassar R. Caspase-3 cleavage of GGA3 stabilizes BACE: implications for Alzheimer's disease. Neuron. 2007; 54:671–673. [PubMed: 17553417]