M. Hosseini, et al. [2010] Med. Hypotheses Res. **6**: 51-59.

REVIEW

Potential Preventions and Treatments of Alzheimer's Disease: A Pathophysiologic Approach

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Abstract. Alzheimer's disease (AD) is the main cause of dementia in elderly worldwide. An important initial step in controlling this disorder includes the experimental verification of the pathophysiologic and mechanistic models. Here we reviewed previous pathophysiologic findings concerning vascular and inflammatory mechanisms, and also proposed a model that may help understand neuronal cell death. According to the suggested model, some potential therapies are discussed. It is suggested that sorafenib, sunitinib maleate, rosiglitazone, antagonists of TNF (adalimumab, etanercept, infliximab, and thalidomide), anakinra, and some other drugs may be beneficial for the prevention or treatment of Alzheimer's disease.

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Received on 09-03-2009; accepted on 05-05-2010.

1. Introduction

Alzheimer's disease (AD) is the most important cause of dementia in old people. Severe brain atrophy related to accumulation of beta-amyloid (Aβ) and neurofibrillary tangles are the main features of this devastating disorder. AD has a predictive pattern of cognitive impairment. Cell death of neurons in AD progresses from the hippocampus and subcortical nuclei, with selective neurotransmitter deficiencies to temporoparietal and then frontal regions, and then to global involvement, respectively [1-4].

Since 1907, when Alzheimer reported first description of neuronal and vascular lesions in this heterogeneous disorder [5], researchers have designed many clinical, epidemiological, and basic science studies to understand and manage this disorder. It seems that one critical step for controlling and managing this disease is the understanding of the pathophysiologic patterns of AD and to draw models for their mechanisms. Based on vascular and inflammatory mechanisms, here we review the previous pathophysiologic findings, and also propose a model which may help interpret accelerated cell death of neurons. Based on this proposed model, some potential therapies are also proposed.

2. A Brief Review of the Previous Findings

Aβ is a cleavage product of the amyloid precursor protein (APP). Processing of APP abnormally into the amyloidogenic fragment, Aβ42, is of important pathological features in AD [6].

Vascular factors can have a role in the pathogenesis of AD [7]. A regionally-increased capillary density was noted in AD [8]. Blood brain barrier (BBB) is a brain structure with high metabolic rate which restricts free passage of solutes between blood and brain interstitial fluids and has a limitation on uncontrolled entry of toxins into the brain. The functional integrity of the capillary unit in the BBB is fundamental for the normal performance and functionality of the brain [9]. Compromised BBB function caused by elevated Aβ could play a major role in AD development and might define an early point of intervention for designing effective therapy for the disease [10]. BBB is severely damaged in the cerebral cortex by excessive exposure to Aβ even in the absence of well defined senile plaques [10].

Microglia, involved in plaque formation, originates from blood monocytes [11, 12]. Application of Aβ in cerebral endothelial cells' environment has been shown to increase transmigration of monocytes across a BBB model in vitro [13, 14]. Recruitment of monocytic lineage cells is the response to chemoattractant Aβ [15, 16]. Increasing in the number of microglia, in association with a raise in the amyloid core size and the absence of any evidence of Aβ internalization in microglia contradicts this hypothesis that microglia remove Aβ. Besides, a large interface between microglia cells and Aβ and the lack of evidence of phagocytosis indicate that microglia in plaques cannot internalize and remove extra cellular deposits of soluble and oligomeric Aβ, but rather can concentrate it and convert it to the fibrillized form [17, 18]. Several roles for microglia in the pathogenesis of AD have been proposed, including the production of Aβ fibrils [19, 20], proteolytic processing of APP [21], synaptic stripping [22], destruction of neurons through complement activation [23], and production of cytokines, nitric oxide, glutamate and neurotoxins [24].

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that is produced by microglia and reactive astrocytes. Levels of TNF-α in cerebrospinal fluid (CSF) are elevated in patients with AD [25]. TNF-α could show its toxic effects at least via two mechanisms. It could increase transforming growth factor-β (TGF-β) levels which itself could promote amyloidogenesis in experimental mice models of AD, indicating that it could be a risk factor for developing AD [26]. Furthermore, TGF-β could increase the connective tissue growth factor (CTGF) levels via

a dependent mechanism [27]. Double immunostaining for TGF-β1 and CTGF revealed the presence of TGF-β1 reactive astrocytes closely associated with CTGF-positive tangle bearing neurons [28]. Results from Ueberham *et al.* indicate a role for CTGF in the process of neurodegeneration in AD [29]. CTGF could play a role in AD. The close association between CTGF and PHF tau observed in the study by Ueberham *et al*. could indicate involvement of CTGF in phosphorylation of tau. Alternatively, it might also play a more direct role in the polymerization process of human tau into PHF [30]. CTGF expression was found to be pressure sensitive in a way that high static pressure induces apoptosis in a CTGF-dependent manner [31].

TNF-α is also known to stimulate vascular endothelial growth factor (VEGF) production [8, 32]. TGF-β which is produced by both gelial and neuronal cells within the brain [33] also stimulates the production of VEGF [34]. The intrathecal levels of VEGF are correlated to clinical severity of AD and to the intrathecal levels of Aβ protein [35]. Also it is indicated that VEGF could have neuroprotective functions [36, 37], but Ueberham *et al.* observed a co-expression of VEGF and CTGF in small blood vessels. This vascular and perivascular source of CTGF might lead to an enhanced binding of VEGF [38], thereby segregating VEGF from it's potentially neuroprotective functioning on neurons. Furthermore, VEGF is a strong inducer of CTGF [28]. VEGF increases permeability of BBB to moderate size molecules (10 kDa) and produces a modest dilation of cerebral arterioles [39]. Murohara *et al.* suggested that VEGF-induced increase in permeability is related to the synthesis/release of nitric oxide, since the inhibitors of nitric oxide synthase attenuate the VEGF-induced increase in vascular permeability [40]. VEGF could increase the flux of calcium across endothelium [41] and it could exert a direct effect on vascular endothelium [42]. Astrocytes regulate extra cellular levels of excitatory amino acids such as glutamate and contribute to homeostasis within the central nervous system. However, in response to stimulation with Aβ42, reactive astrocytes can produce TGF-β, TNF-α and interleukin 1 (IL-1) [43, 44]. Furthermore, these dysfunctional Aβ activated astrocytes could also release reactive oxygen species (ROS) which in turn contribute to the inflammation process and also cause the degeneration of the nearby neurons [6]. IL-6 which could be produced by microglia and reactive astrocytes could also be a pathogenic pro-inflammatory cytokine [45, 46]. Some of the known pathological effects of IL-1 are listed below [47]:

- Induction of α1-antichemotrypsin overexpression in astrocytes [48], which is co-deposited in Aβ plaques in AD [49].
- Induction of neuronal synthesis and processing of the APP [50, 51], thus favoring the release of both amyloid peptide fragments (and further deposition of Aβ) and gliotrophic [52] secreted fragments of the APP.
- Overexpression of neuronal acetyl cholinesterase [53].
- Induction of S100β, which then leads to other effects, such as augmentation of the astrocytic nitric oxide synthase activity [54] accompaied by the release of potentially neurotoxic nitric oxide, induction of neuronal APP and IL-6 production [55, 56], and induction of astrocytic IL-1β expression [57].

3. Potential Preventions and Drug Therapies

Based on the above-mentioned findings, we proposed a model depicting the interactions of different local mediators in AD (**FIG 1**). This model appreciates the complex relationships and interactions of these mediators in AD, and it also logically leads to the consideration of the use of various medical treatments. According to the proposed model, a number of drugs which could antagonize the effect of pathogenic mediators could be potentially beneficial and inhibit or slow down the progression of AD.

VEGF. VEGF exerts its effects via tyrosine kinase receptors. Agents which could inhibit its

TABLE 1. Proposed drugs for prevention and/or treatment of Alzheimer's disease.

Proposed drug	Potential therapeutic mechanism
Sorafenib	Inhibits VEGF signaling
Sunitinib maleate	inhibits VEGF signaling
Bevacizumab	monoclonal antibody against VEGF
Rosiglitazone	decreases IL-6
Infliximab	monoclonal antibody against TNF-α
Etanercept	TNF type 2 receptor fused to IgG1
Adalimumab	Human antibody to TNF
Thalidomide	inhibits TNF-α synthesis; Immuno-modulator
Anakinra	recombinant IL-1 receptor antagonist
rhAPC	down-regulates the expression of IL-6 and TNF-α; profibrinolytic effect
Oltipraz	antioxidant

signaling could antagonize its angiogenic effects. Sorafenib and Sunitinib maleate, which are used for treating some cancers such as metastatic renal cell carcinoma and advanced gastrointestinal stromal tumors [58, 59] inhibit VEGF signaling through tyrosine kinase receptors [60,61]. Bevacizumab which is a recombinant humanized monoclonal antibody against VEGF and is approved for treating advanced colorectal cancer [62] could also antagonize the effects of VEGF [63].

IL-6. As mentioned in this paper, levels of pro-inflammatory cytokine IL-6 is elevated in AD. Rosiglitazone is one of the insulin sensitizing agents for treating diabetes mellitus. There are some evidences that show the effect of rosiglitazone in decreasing levels of IL-6 [64]. Therefore, we recently hypothesized that this drug may have a therapeutic effect on AD through reducing IL-6 [65].

TNF-α. Biological agents that bind to and neutralize the TNF-α are widely noted for treating inflammatory diseases. These drugs are: etanercept, a TNF type 2 receptor fused to IgG1 and is assessed to be effective in psoriasis [66]; infliximab, a chimeric mouse-human monoclonal antibody against TNF, which has passed successful trials for treating rheumatoid arthritis [67]; adalimumab, a fully human antibody to TNF, which is used in cutaneous sarcoidosis [68]; thalidomide, which has immuno-modulatory and anti inflammatory effects such as inhibition of TNF-α synthesis and is effective for treating Behçet's syndrome [69].

IL-1. Anakinra, a recombinant antagonist against IL-1 receptor, has recently been introduced for treating some rheumatic diseases [70]. Since the pathogenesis of AD is partly based on this pro-inflammatory cytokine, anakinra may have therapeutic effect in AD.

Antioxidants. Oxidative stress is believed to have critical roles in neurodegenerative diseases including AD [71]. Reactive oxygen species are produced during oxidative reactions which could in turn impair various membrane proteins participating in ion homeostasis [72, 73]. For example, they could change the channels involved in calcium homeostasis such as N-methyl-D-aspartate (NMDA) receptor channels or ion motive adenosine triphosphatases [72]. The subsequent increase in intracellular calcium, along with the accumulation of ROS could damage cellular components such as membrane lipids, proteins and DNA, and finally results in apoptosis of neurons. Therefore, trying to fight against oxidative stress is shown to have preventive and therapeutic effects in AD. For example, vitamin E [74], selegiline [75], and ginkgo biloba [76] could be beneficial in AD. Oltipraz, a synthetic analogue of 1,2-dithiole-3-thione with antioxi-

dant properties, was recently suggested to be useful in the prevention of AD [77].

Recombinant human activated protein C (rhAPC) has shown its effectiveness in severe sepsis through its profibrinolytic and anti-inflammatory activity [78, 79]. Studies have suggesting that APC has direct anti-inflammatory activity by down regulating the expression of inflammatory cytokines such as IL-1 and TNF-α [80-84]. Although some studies which assessed the effects of this drug did not found the levels of TNF-α, IL-6 and IL-1β to be decreased significantly in severe sepsis and endotoxemia models [85-87, 79]. One possibility is that the function of rhAPC is to reduce the biomarkers of inflammation at a local level and that these changes are not detected in peripheral blood. Hence, rhAPC due to its anti-inflammatory and profibrinolytic effects could be beneficial in AD.

Although vascular dementia (VD) and AD are two different disorders [88], researchers suggest that VD could interact synergistically with AD to increase the possibility of clinically expressed dementia [89]. Moreover, post-mortem studies suggest that the presence of even small amounts of infarct brain tissue can substantially amplify the effects of AD neuropathology on cognition, particularly when the AD changes are mild [90-92]. Therefore, rhAPC profibrinolytic effects could be useful.

Management of hypertension. As mentioned above, high static pressure induces apoptosis in a CTGF-dependent manner [31]. In addition, we recently hypothesized that acute hypertensive crisis such as pheochromocytoma and acute post-operative hypertension may be risk factors for induction and progression of AD [93]. Our hypothesis originated from studies in mouse models which showed that acutely induced hypertension induces a breaking in the BBB and reactive astrocytosis and evokes trigger factors of neurodegeneration such as oxidative stress and inflammation [94]. Therefore, it further suggests that BBB impairment could be at least in part a pathogenic factor for AD. Good management of hypertension (including life style modification, low salt and fat, fiber rich-diet, exercise and medical therapy) may protect against AD. Reactive oxygen species produced by reactive astrocytes in response to high blood pressure may play a pathogenic role.

Targeting other risk factors. Researchers have shown that apoptotic-like processes may be involved in some of the neuronal losses in Alzheimer's disease [95]. Stoothoff and Johnson have shown that osmotic stress results in apoptosis in human neuroblastomal cells [96]. Hence, we proposed that chronic dehydration states such as hyperglycemic hyperosmolar state of diabetes mellitus Laxative and diuretic overuse or abuse, through induction of brain neuronal cell apoptosis, could be risk factors for AD [97].

Arsenic and its compounds are used in pesticides, insecticides, herbicides and some kinds of alloys. This pollutant can induce apoptosis in rat cortical neurons. This process is based on the activation of c-Jun N-terminal kinase 3 (JNK3) and p38 mitogen activated protein kinase (P38 MAPK) by arsenic [98]. Accordingly, we recommend that arsenic (via activating the p38 MAPK and JNK3) which may cause brain neuronal apoptosis, may lead to Alzheimer's disease [99].

4. Conclusion

In summary, we have discussed a descriptive model for the treatment of AD, on the basis of some of the known or proposed pathophysiologic mechanisms. According to this model, some potential approaches for its management are also discussed (summarized in **TABLE 1**). Certainly, these proposed treatments rest to be assessed experimentally and clinically before they can be used clinically.

References

1. **Cummings JL** [2004] Alzheimer's disease. N Engl J Med 351: 56-67.
2. **Groves WC, Brandt J, Steinberg M, Warren A, Rosenblatt A, Baker A, Lyketsos CG** [2000] Vascular dementia and Alzheimer's disease: is there a difference? A

comparison of symptoms by disease duration. J Neuropsychiatry Clin Neurosci 12: 305-315.
3. **LaFerla FM, Oddo S** [2005] Alzheimer's disease: Abeta, tau and synaptic dysfunction. Trends Mol Med 11: 170-176.
4. **Masters CL, Cappai R, Barnham KJ, Villemagne VL** [2006] Molecular mechanisms for Alzheimer's disease: implications for neuroimaging and therapeutics. J Neurochem 97: 1700-1702.
5. **Alzheimer A** [1907] uber eine eigenartig Erkrankung der hirnrinde. Allg Z Psychiatrie Psych Ger Med 64: 146-148.
6. **Johnstone M, Gearing AJ, Miller KM** [1999] A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. J Neuroimmunol 93: 182-93.
7. **Kalaria RN** [1996] Cerebral vessels in ageing and Alzheimer's disease. Pharmacol Ther 72: 193-214.
8. **McCourt M, Wang JH, Sookhai S, Redmond HP** [1999] Proinflammatory mediators stimulate neutrophil-directed angiogenesis. Arch Surg 134: 1325-1331 (discussion on 1331-1332).
9. **Zlokovic BV** [2005] Neurovascular mechanisms of Alzheimer's neurodegeneration. Trends Neurosci 28: 202-208.
10. **Ujiie M, Dickstein DL, Carlow DA, Jefferies WA** [2003] Blood-brain barrier permeability precedes senile plaque formation in an Alzheimer disease model. Microcirculation 10: 463-470.
11. **Hickey WF, Kimura H** [1988] Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. Science 239: 290-292.
12. **Lawson LJ, Perry VH, Gordon S** [1992] Turnover of resident microglia in the normal adult mouse brain. Neuroscience 48: 405-415.
13. **Fiala M, Zhang L, Gan X, Sherry B, Taub D, Graves MC, Hama S, Way D, Weinand M, Witte M, Lorton D, Kuo YM, Roher AE** [1998] Amyloid-beta induces chemokine secretion and monocyte migration across a human blood-brain barrier model. Mol Med 4: 480-489.
14. **Giri R, Shen Y, Stins M, Du Yan S, Schmidt AM, Stern D, Kim KS, Zlokovic B, Kalra VK** [2000] beta-Amyloid-induced migration of monocytes across human brain endothelial cells involves RAGE and PECAM-1. Am J Physiol Cell Physiol 279: C1772-C1781.
15. **Wang HY, D'Andrea MR, Nagele RG** [2002] Cerebellar diffuse amyloid plaques are derived from dendritic Abeta42 accumulations in Purkinje cells. Neurobiol Aging 23: 213-223.
16. **Hansson E, Rönnbäck L** [2003] Glial neuronal signaling in the central nervous system. FASEB J 17: 341-348.
17. **Wegiel J, Wang KC, Imaki H, Rubenstein R, Wronska A, Osuchowski M, Lipinski WJ, Walker LC, LeVine H** [2001] The role of microglial cells and astrocytes in fibrillar plaque evolution in transgenic APP(SW) mice. Neurobiol Aging 22: 49-61.
18. **Wegiel J, Imaki H, Wang KC, Wegiel J, Wronska A, Osuchowski M, Rubenstein R** [2003] Origin and turnover of microglial cells in fibrillar plaques of APPsw transgenic mice. Acta Neuropathol 105: 393-402.
19. **Frackowiak J, Wisniewski HM, Wegiel J, Merz GS, Iqbal K, Wang KC** [1992] Ultrastructure of the microglia that phagocytose amyloid and the microglia that produce beta-amyloid fibrils. Acta Neuropathol 84: 225-233.
20. **Wisniewski HM, Weigel J** [1993] Migration of perivascular cells into the neuropil and their involvement in beta-amyloid plaque formation. Acta Neuropathol 85: 586-595.
21. **Cras P, Kawai M, Siedlak S, Mulvihill P, Gambetti P, Lowery D, Gonzalez-DeWhitt P, Greenberg B, Perry G** [1990] Neuronal and microglial involvement in beta-amyloid protein deposition in Alzheimer's disease. Am J Pathol 137: 241-246.
22. **Nieto-Sampedro M, Mora F** [1994] Active microglia, sick astroglia and Alzheimer type dementias. Neuroreport 5: 375-380.
23. **Klegeris A, McGeer PL** [2007] Complement activation by islet amyloid polypeptide (IAPP) and alpha-synuclein 112. Biochem Biophys Res Commun 357: 1096-1099.
24. **Lipton SA, Gu Z, Nakamura T** [2007] Inflammatory mediators leading to protein misfolding and uncompetitive/fast off-rate drug therapy for neurodegenerative disorders. Int Rev Neurobiol 82: 1-27.
25. **Tarkowski E, Blennow K, Wallin A, Tarkowski A** [1999] Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. J Clin Immunol 19: 223-230.
26. **Wyss-Coray T, Masliah E, Mallory M, McConlogue L, Johnson-Wood K, Lin C, Mucke L** [1997] Amyloidogenic role of cytokine TGF-beta1 in transgenic mice and in Alzheimer's disease. Nature 389: 603-606.
27. **Heusinger-Ribeiro J, Eberlein M, Wahab NA, Goppelt-Struebe M** [2001] Expression of connective tissue growth factor in human renal fibroblasts: regulatory roles of RhoA and cAMP. J Am Soc Nephrol 12: 1853-1861.
28. **Ueberham U, Ueberham E, Gruschka H, Arendt T** [2003] Connective tissue growth factor in Alzheimer's disease. Neuroscience 116: 1-6.
29. **Arendt T** [2001] Disturbance of neuronal plasticity is a critical pathogenetic event in Alzheimer's disease. Int J Dev Neurosci 19: 231-245.
30. **Bhattacharya K, Rank KB, Evans DB, Sharma SK** [2001] Role of cysteine-291 and cysteine-322 in the polymerization of human tau into Alzheimer-like filaments. Biochem Biophys Res Commun 285: 20-26.
31. **Hishikawa K, Oemar BS, Nakaki T** [2001] Static pressure regulates connective tissue growth factor expression in human mesangial cells. J Biol Chem 276: 16797-16803.
32. **Thomas KA** [1996] Vascular endothelial growth factor, a potent and selective angiogenic agent. J Biol Chem 271: 603-606.
33. **Pratt BM, McPherson JM** [1997] TGF-beta in the central nervous system: potential roles in ischemic injury and

34. **Koochekpour S, Merzak A, Pilkington GJ** [1996] Vascular endothelial growth factor production is stimulated by gangliosides and TGF-beta isoforms in human glioma cells in vitro. Cancer Lett 102: 209-215.
35. **Tarkowski E, Issa R, Sjögren M, Wallin A, Blennow K, Tarkowski A, Kumar P** [2002] Increased intrathecal levels of the angiogenic factors VEGF and TGF-beta in Alzheimer's disease and vascular dementia. Neurobiol Aging 23: 237-243.
36. **Kalaria RN, Cohen DL, Premkumar DR, Nag S, LaManna JC, Lust WD** [1998] Vascular endothelial growth factor in Alzheimer's disease and experimental cerebral ischemia. Brain Res Mol Brain Res 62: 101-105.
37. **Jin KL, Mao XO, Greenberg DA** [2000] Vascular endothelial growth factor: direct neuroprotective effect in in vitro ischemia. Proc Natl Acad Sci USA 97: 10242-10247.
38. **Inoki I, Shiomi T, Hashimoto G, Enomoto H, Nakamura H, Makino K, Ikeda E, Takata S, Kobayashi K, Okada Y** [2002] Connective tissue growth factor binds vascular endothelial growth factor (VEGF) and inhibits VEGF-induced angiogenesis. FASEB J 16: 219-221.
39. **Mayhan WG** [1999] VEGF increases permeability of the blood-brain barrier via a nitric oxide synthase/cGMP-dependent pathway. Am J Physiol 276(5 Pt 1): C1148-C1153.
40. **Murohara T, Horowitz JR, Silver M, Tsurumi Y, Chen D, Sullivan A, Isner JM** [1998] Vascular endothelial growth factor/vascular permeability factor enhances vascular permeability via nitric oxide and prostacyclin. Circulation. 97: 99-107.
41. **Bates DO, Curry FE** [1997] Vascular endothelial growth factor increases microvascular permeability via a Ca(2+)-dependent pathway. Am J Physiol 273(2 Pt 2): H687-H694.
42. **Hippenstiel S, Krüll M, Ikemann A, Risau W, Clauss M, Suttorp N** [1998] VEGF induces hyperpermeability by a direct action on endothelial cells. Am J Physiol 274(5 Pt 1): L678-L684.
43. **Apelt J, Schliebs R** [2001] Beta-amyloid-induced glial expression of both pro- and anti-inflammatory cytokines in cerebral cortex of aged transgenic Tg2576 mice with Alzheimer plaque pathology. Brain Res 894: 21-30.
44. **Smits HA, Rijsmus A, van Loon JH, Wat JW, Verhoef J, Boven LA, Nottet HS** [2002] Amyloid-beta-induced chemokine production in primary human macrophages and astrocytes. J Neuroimmunol 127: 160-168.
45. **Lue LF, Rydel R, Brigham EF, Yang LB, Hampel H, Murphy GM Jr, Brachova L, Yan SD, Walker DG, Shen Y, Rogers J** [2001] Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro. Glia 35: 72-79.
46. **Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, White CL 3rd, Araoz C** [1989] Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci USA 86: 7611-7615.
47. **Mrak RE, Griffinbc WS** [2001] The role of activated astrocytes and of the neurotrophic cytokine S100B in the pathogenesis of Alzheimer's disease. Neurobiol Aging 22: 915-922.
48. **Das S, Potter H** [1995] Expression of the Alzheimer amyloid-promoting factor antichymotrypsin is induced in human astrocytes by IL-1. Neuron 14: 447-456.
49. **Abraham CR, Selkoe DJ, Potter H** [1988] Immunochemical identification of the serine protease inhibitor alpha 1-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. Cell 52: 487-501.
50. **Forloni G, Demicheli F, Giorgi S, Bendotti C, Angeretti N** [1992] Expression of amyloid precursor protein mRNAs in endothelial, neuronal and glial cells: modulation by interleukin-1. Brain Res Mol Brain Res 16: 128-134.
51. **Tachida Y, Nakagawa K, Saito T, Saido TC, Honda T, Saito Y, Murayama S, Endo T, Sakaguchi G, Kato A, Kitazume S, Hashimoto Y** [2008] Interleukin-1beta up-regulates TACE to enhance alpha-cleavage of APP in neurons: resulting decrease in Abeta production. J Neurochem 104: 1387-1393.
52. **Barger SW, Harmon AD** [1997] Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. Nature 388: 878-881.
53. **Li Y, Liu L, Kang J, Sheng JG, Barger SW, Mrak RE, Griffin WS** [2000] Neuronal-glial interactions mediated by interleukin-1 enhance neuronal acetylcholinesterase activity and mRNA expression. J Neurosci 20: 149-155.
54. **Hu J, Castets F, Guevara JL, Van Eldik LJ** [1996] S100 beta stimulates inducible nitric oxide synthase activity and mRNA levels in rat cortical astrocytes. J Biol Chem 271: 2543-2547.
55. **Li Y, Barger SW, Liu L, Mrak RE, Griffin WS** [2000] S100beta induction of the proinflammatory cytokine interleukin-6 in neurons. J Neurochem 74: 143-150.
56. **Li Y, Wang J, Sheng JG, Liu L, Barger SW, Jones RA, Van Eldik LJ, Mrak RE, Griffin WS** [1998] S100 beta increases levels of beta-amyloid precursor protein and its encoding mRNA in rat neuronal cultures. J Neurochem 71: 1421-1428.
57. **Hu J, Van Eldik LJ** [1999] Glial-derived proteins activate cultured astrocytes and enhance beta amyloid-induced glial activation. Brain Res 842: 46-54.
58. **Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG** [2006] Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 368: 1329-1338.
59. **Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA** [2007] Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356: 115-124.
60. **Strumberg D, Clark JW, Awada A, Moore MJ, Richly**

H, Hendlisz A, Hirte HW, Eder JP, Lenz HJ, Schwartz B [2007] Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. Oncologist 12: 426-437.

61. **Roskoski R Jr** [2007] Sunitinib: a VEGF and PDGF receptor protein kinase and angiogenesis inhibitor. Biochem Biophys Res Commun 356: 323-328.
62. **Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F** [2004] Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350: 2335-2342.
63. **Bock F, Onderka J, Dietrich T, Bachmann B, Kruse FE, Paschke M, Zahn G, Cursiefen C** [2007] Bevacizumab as a potent inhibitor of inflammatory corneal angiogenesis and lymphangiogenesis. Invest Ophthalmol Vis Sci48: 2545-2552.
64. **Esposito K, Ciotola M, Carleo D, Schisano B, Saccomanno F, Sasso FC, Cozzolino D, Assaloni R, Merante D, Ceriello A, Giugliano D** [2006] Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. Diabetes Care 29: 1071-1076.
65. **Gharibzadeh S, Hoseini SS** [2007] A novel view on the pharmacodynamics of rosiglitazone and introducing some potential drugs in ameliorating Alzheimer's disease. J Neuropsychiatry Clin Neurosci 19: 349.
66. **Bos JD, de Korte J** [2006] Effects of etanercept on quality of life, fatigue, and depression in psoriasis. Lancet 367: 6-7.
67. **Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI, Drosos AA** [2005] Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med 118: 515-520.
68. **Heffernan MP, Smith DI** [2006] Adalimumab for treatment of cutaneous sarcoidosis. Arch Dermatol 142: 17-19.
69. **Sayarlioglu M, Kotan MC, Topcu N, Bayram I, Arslanturk H, Gul A** [2004] Treatment of recurrent perforating intestinal ulcers with thalidomide in Behçet's disease. Ann Pharmacother 38: 808-811.
70. **Lovell DJ, Bowyer SL, Solinger AM** [2005] Interleukin-1 blockade by Anakinra improves clinical symptoms in patients with neonatal-onset multisystem inflammatory disease. Arthritis Rheum 52: 1283-1286.
71. **Felician O, Sandson TA** [1999] The neurobiology and pharmacotherapy of Alzheimer's disease. J Neuropsychiatry Clin Neurosci 11: 19-31.
72. **Mark RJ, Hensley K, Butterfield DA, *et al.*** [1995] Amyloid beta-peptide impairs ion-motive ATPase activities: evidence for a role in loss of neuronal Ca^{2+} homeostasis and cell death. J Neurosci 15: 6239-6249.
73. **Mattson MP, Rydel RE** [1996] Amyloid ox-tox transducers. Nature 382: 674-675
74. **Grundman M** [2000] Vitamin E and Alzheimer disease: the basis for additional clinical trials. Am J Clin Nutr 71: 630S-636S.
75. **Filip V, Kolibás E** [1999] Selegiline in the treatment of Alzheimer's disease: a long-term randomized placebo-controlled trial. Czech and Slovak Senile Dementia of Alzheimer Type Study Group. J Psychiatry Neurosci 24: 234-243.
76. **Oken BS, Storzbach DM, Kaye JA** [1998] The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. Arch Neurol 55: 1409-1415.
77. **Gharibzadeh S, Hoseini SS, Mahdavi S** [2007] Oltipraz may be useful in the prevention or treatment of Alzheimer's disease. Med Hypotheses 68: 915-916.
78. **Macias WL, Yan SB, Williams MD, Um SL, Sandusky GE, Ballard DW, Planquois JM**. [2005] New insights into the protein C pathway: potential implications for the biological activities of drotrecogin alfa (activated). Crit Care 9 (Suppl 4): S38-S45.
79. **Hughes M** [2006] Recombinant human activated protein C. Int J Antimicrob Agents 28: 90-94.
80. **Murakami K, Okajima K, Uchiba M, Johno M, Nakagaki T, Okabe H, Takatsuki K** [1997] Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production. Am J Physiol 272: L197-L202.
81. **Grey ST, Tsuchida A, Hau H, Orthner CL, Salem HH, Hancock WN** [1994] Selective inhibitory effects of the anticoagulant activated Protein C on the responses of human mononuclear phagocytes to LPS, IFN-γ, or phorbol ester. J Immunol 153: 3664-3672.
82. **Hancock WW, Tsuchida A, Hau H, Thomson NM, Salem HH**: [1992] The anticoagulants Protein C and Protein S display potent anti-inflammatory and immunosuppressive effects relevant to transplant biology and therapy. Transplant Proc 24: 2302-2303.
83. **White B, Schmidt M, Murphy C, Livingstone W, O'Toole D, Lawler M, O'Neill L, Kelleher D, Schwarz HP, Smith OP** [2000] Activated protein C inhibits lipopolysaccharide-induced nuclear translocation of nuclear factor κB (NF-κB) and tumor necrosis factor alpha (TNF-alpha) production in the THP-1 monocyte cell line. Br J Haematol 110: 130-134.
84. **Hancock WW, Grey ST, Hau L, Akalin E, Orthner C, Sayegh MH, Salem HH** [1995] Binding of activated protein C to a specific receptor on human mononuclear phagocytes inhibits intracellular calcium signaling and monocyte-dependent proliferative responses. Transplantation 60: 1525-1532.
85. **Smirnov MD, Pyzh MV, Borovikov DV, Atorozhilova AN, Dobrovolsky AB, Golubych VL, Gratsiansky NA** [1991] Low doses of activated Protein C delay arterial thrombosis in rats. Thrombosis Res 57: 645-650.
86. **Derhaschnig U, Reiter R, Knobl P, Baumgartner M, Keen P, Jilma B** [2003] Recombinant human activated protein C has minimal effect on markers of coagulation, fibrinolysis, and inflammation in acute human endotoxemia. Blood 102: 2093-2098.
87. Kalil **AC, Coyle SM, Um JY, LaRosa SP, Turlo MA, Calvano SA, Sundin DP, Nelson DR, Lowry SF** [2004]

Effects of drotrecogin alfa (activated) in human endotoxemia. Shock 21: 222-229.

88. **Groves WC, Brandt J, Steinberg M, Warren A, Rosenblatt A, Baker A, Lyketsos CG** [2000] Vascular dementia and Alzheimer's disease: is there a difference? A comparison of symptoms by disease duration. J Neuropsychiatry Clin Neurosci 12: 305-315.
89. **Decarli C** [2004] Vascular factors in dementia: an overview. J Neurol Sci 226: 19-23.
90. **Esiri MM, Wilcock GK, Morris J** [1997] Neuropathological assessment of the lesions of significance in vascular dementia. J Neurol Neurosurg Psychiatry 63: 749-753.
91. **Schneider JA, Wilson RS, Cochran EJ, Bienias JL, Arnold SE, Evans DA, Bennett DA** [2003] Relation of cerebral infarctions to dementia and cognitive function in older persons. Neurology 60: 1082-1088.
92. **Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR** [1997] Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277: 813-817.
93. **Gharibzadeh S, Hoseini SS, Mahdavi S** [2007] Acute hypertensive crisis may be a risk factor for Alzheimer's disease induction and progression. J Neuropsychiatry Clin Neurosci 19: 483-484.
94. **Poulet R, Gentile MT, Vecchione C, Distaso M, Aretini A, Fratta L, Russo G, Echart C, Maffei A, De Simoni MG, Lembo G** [2006] Acute hypertension induces oxidative stress in brain tissues. J Cereb Blood Flow Metab 26: 253-262.
95. **Friedlander RM** [2003] Apoptosis and caspases in neurodegenerative diseases. N Engl J Med 348: 1365-1375.
96. **Stoothoff WH, Johnson GV** [2001] Hyperosmotic stress-induced apoptosis and tau phosphorylation in human neuroblastoma cells. J Neurosci Res 65: 573-582.
97. **Gharibzadeh S, Hoseini SS** [2007] Chronic dehydration may be a preventable risk factors for Alzheimer's disease. Med Hypotheses 68: 718.
98. **Namgung U, Xia Z** [2001] Arsenic induces apoptosis in rat cerebellar neurons via activation of JNK3 and p38 MAP kinases. Toxicol Appl Pharmacol 174: 130-138.
99. **Gharibzadeh S, Hoseini SS** [2008] Arsenic exposure may be a risk factor for Alzheimer's disease. J Neuropsychiatry Clin Neurosci 20: 501.