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Letter to the editor

Glutathione (Gsh) as a Biomarker for Brain Research [$^{1}_{a-b}$]

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Dysregulation of glutathione homeostasis and alterations in glutathione-dependent enzyme activities are increasingly implicated in the induction and progression of neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, and Friedreich's ataxia [2].Various lines of evidence indicate that brain OS (Oxidative Stress) is a key underlying factor behind AD etiology. GSH levels have been consistently shown to reflect OS status. Furthermore, the literature reviewed thus far reveals a strong correlation between AD pathology and reduced GSH levels. These findings have spurred the development of assays for GSH levels as a biomarker for AD. Several methodologies have been developed to assess GSH levels in peripheral biological samples, such as blood. Recent progress in technology has also enabled noninvasive in vivo measurement of GSH directly in different brain regions using MRS. We discuss the latest findings from studies utilizing these various GSH measurement methodologies and evaluate their relative potential in serving as a reliable measure of GSH levels. The detection of unregular developments in the living brain may aid neurodegenerative diseases research and drug developments that will afforda remedy to millions. In this letter we report on the availability of a leveling agent that is introduced into the living brain via an injection to the bloodstream. It penetrates the Blood-Brain Barrier and enables preferential preferentially staining of the hippocampus inner brain gland with fluorescent laser dye, a synbimane moiety. One may find notes on the suggestions for New Blood Test to Accurately Detect Early-Stage Alzheimer's, examples are available on the web [3]. We suggest to measure Two-photon laser scanning microscopy (TPLSM) to directly measure glutathione (GSH) as its fluorescent glutathione S-Bimane conjugate (GSB) in blood samples after injection of the AIB-CYSBIMINI (has an analog of S-bimanylmercaptoacetic acid as a moiety in the probe), followed by the sleep of the animal. A Decrease in GSH is indicative of Oxidative Stress (OS). Oxidative stress and the diminishing Glutathione as a result of this early process suggest that Glutathione can be viewed as a molecular whistleblower for Alzheimer's disease [4].

Discussion

There is no remedy today. One of the prevailing hypothesis is the Amyloid hypothesis [5]. The genetic perspective. There is a series of events that may spread over decades in the patient brain before dementia is recognized. "According to the amyloid (Aβ) hypothesis, accumulation of Aβ in the brain is the primary influence driving AD pathogenesis. The rest of the disease process, including the formation of neurofibrillary tangles containing tau protein, is proposed to result from an imbalance between Aβ production and Aβ clearance" [6]. Excessive amyloid-β (Aβ) deposition in the brain is one of the most crucial events in the early pathological stage of Alzheimer's disease (AD). Therefore, Aβ deposits have enough potential to become a useful biomarker for not only an early diagnosis of AD, but also for the assessment of the clinical efficacy of anti-Aβ therapies, if they can be measured non-invasively and reliably in living patients [7]. In the past, the presence of an efflux system in mouse cerebral micro vessel endothelial cells was examined in vitro by using fluorescent glutathione-bimane (GS-B) conjugate [8,9]. In order to enable development of novel therapeutically agents to treat the AD before dementia is observed, an instrumental diagnosis of the situation in the earliest stages, just when amyloid beta deposits start to accumulate, a potent candidate technique to measure this biomarker has to be developed. Nedergaard [4a] has shown that while asleep, the brain of mice is excreting the unwanted "trash metabolites" is crossing back the BBB, from the brain to the outer fluids ending in the blood system and is excreted from the organism in the usual way through the liver. In her case, Fluorescent agents had to be injected to the brain which allowed follow-up by two-photon spectrophotometry. Our idea was to design and prepare an agent that would be injected to the blood system and penetrate the BBB, combine with the biomarkers Aβ, or Glutathione [10,11,12] in the inner brain (hippocampus, entorhinal

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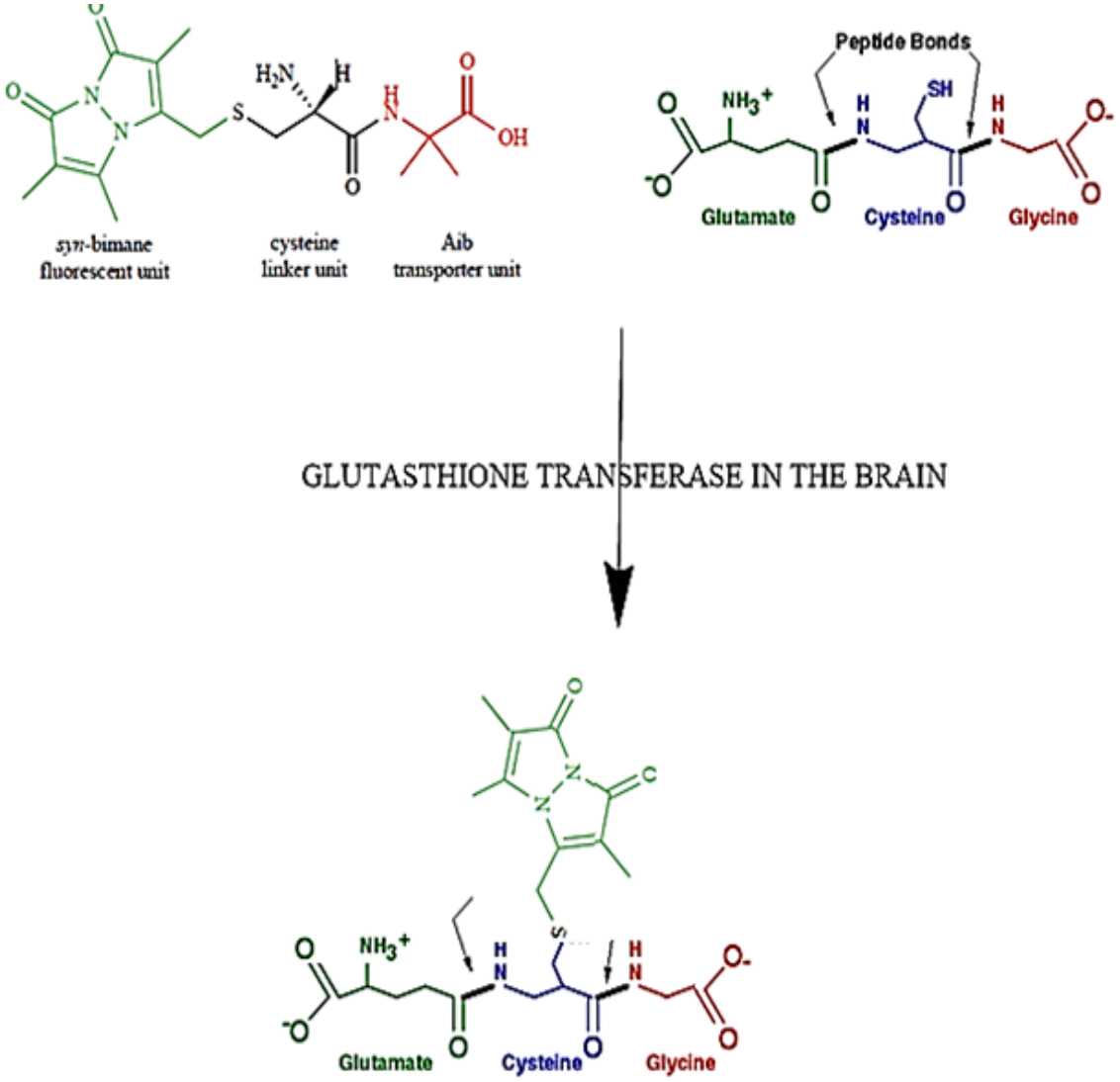

Fluorescent Indicator for Glutathione in the Brain Excreted (Nedergaard) At Sleep

cortex, substantia innominate, the EC-hippocampus system)and will allow two photons spectroscopically measurements of the outer flux liquid being excreted from the brain while asleep. In this way, the Aβ accumulated in the brain before the excretion will serve as biomarkers for the early stages of AD. To examine Brain Fluids were used two-photon imaging of monochlorobimane [13] fluorescence and high levels of glutathione were established [14]. The fact that AIB (alpha-amino iso butyric acid) could cross the BBB was established by Fenstermacher [15] and was applied for research and introduction of drugs into the rats' brain [16]. Gazit has applied a Try-Aib dipeptide as an agent to mark the brain of rats [17]. Investigators would like to pursue the idea that AD could be cured with peptides and their mimics [18]. The penetration of drugs into the brain is critical for any approach to the development of drugs and cure of AD [19]. As a crucial issue for the attempt to discover a cure for the disease, modern methods based on optical sensors which will allow a quantitative follow-up on the cure of the disease, become very attractive [20]. The optical analysis of Aβ (or another polypeptide) from the reflux solution emerging at sleep might become very useful. In 2008, Larbanoix et al. Aβ (or another polypeptide) binding peptides using a random disulfide constrained heptapeptide phage display library [21]. However, the bonding between the heptapeptide to the polypeptide should be leveled with a dye, preferable a laser dye, to enable the follow-up in the reflux fluids from the brain provided this bonding should become instrumental. The transfer of as many moiety from anS-bimanylmercaptoacetic acid as the N-terminal residue has been used in many investigations to mark polypeptides *in vivo*.

References

1.

a) Sun X, Shih AY, Johannssen HC, Erb H, Li P, et al (2006) Two-photon Imaging of Glutathione Levels in Intact Brain Indicates Enhanced Redox Buffering in Developing Neurons and Cells at the Cerebrospinal Fluid and Blood-Brain Interface, The Journal of Biological Chemistry 281(25): 17420–17431.

b) Pocernich CB, Butterfield DA (2012) Elevation of glutathione as a therapeutic strategy in Alzheimer disease, Biochimica et Biophysica Acta 1822(5): 625–630.

2. Johnson WM, Wilson-Delfosse AL, Mieyal JJ (2012) Dysregulation of Glutathione Homeostasis in Neurodegenerative Diseases, Nutrients 4(10): 1399-1440.

3. (2016) New Blood Test To Accurately Detect Early-Stage Alzheimer's. Health | Press Trust of India.

4.

a. Lulu Xie, Hongyi Kang, Qiwu Xu, Michael J. Chen (2013) " Sleep Drives Metabolite Clearance from the Adult Brain": Published in final edited form as: Science 342(6156): doi:10.1126/science.1241224

b. Mueller SG, Weinera MW, Thal LJ, Petersen RC, Jack CR, et al (2005) " Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI)": Alzheimers Dement 1(1): 55–66.

c. Pocernich CB, Butterfield DA (2012) "Elevation of Glutathione as a Therapeutic Strategy in Alzheimer Disease": Biochim Biophys Acta 1822(5): 625–630. doi:10.1016/j.bbadis.2011.10.003

d. Perry TL, Godin DV, SHansen S (1982) Parkinson's disease: A disorder due to nigral glutathione deficiency?, Neuroscience Letters 33(3): 305–310.

e. Migliore L, Fontanaa I, Colognatoa R, Coppedea F, Sicilianob G, et al (2005) Searching for the role and the most suitable biomarkers of oxidative stress in Alzheimer's disease and in other neurodegenerative diseases, Neurobiology of Aging 26(5): 587–595.

5. Tanzi RE and Bertra K (2005) " Twenty Years of the Alzheimer's Review Disease Amyloid Hypothesis: A Genetic Perspective": Cell 120(4): 545–555.

6. Hardy J and Selkoe DJ (2002) " The Amyloid Hypothesis of Alzheimer's disease: Progress and Problems on the Road to Therapeutics". Science 297(5580): 353-356.

7. Furumotoa S, Okamura N, Iwata R, Yanai K, Arai H, et al (2007) " Recent Advances in the Development of Amyloid Imaging Agents": Current Topics in Medicinal Chemistry 7(18): 1773-1789.

8. Homma M, Suzuki H, Kusuhara H, Naito M, Tsuruo T, et al (1999) High-Affinity Efflux transport system for glutathione conjugates on the luminal membrane of a mouse brain capillary endothelial cell line (MBEC4). J. Pharmacol. Exp. Ther 288(1), 198-203.

9. Keelan J, Allen NJ, Antcliffe D, Pal S, Duchen MR (2001) Quantitative imaging of glutathione in hippocampal neurons and glia in culture using monochlorobimane. J. Neurosci. Res 66(5): 873-884.

10. Sumiti S, Mandal P K (2014)" The Emerging Role of Glutathione in Alzheimer's Disease": Journal of Alzheimer's disease 40(3): 519-529.

11. Voelkel W, Sicilia T, Paehler A, Gsell W, Tatschner T, et al (2006) " Increased brain levels of 4-hydroxy-2-nonenal glutathione conjugates in severe Alzheimer's disease": Neurochemistry International 48(8): 679–686.

12. John R. Silvius (1999Fluorescence Measurement of Lipid-Binding Affinity and Interbilayer Transfer of Bimane-Labeled Lipidated Peptides: Protein Lipidation Protocols 116: 177-186.

13. Sun X, Shih AY, Johannssen HC, Erb H, Li P, et al (2006)" Two-photon Imaging of Glutathione Levels in Intact Brain Indicates Enhanced Redox Buffering in Developing Neurons and Cells at the Cerebrospinal Fluid and Blood-Brain Interface,": J Biol Chem 281(25): 17420–17431.

14. Gross PM, Blasberg RG, Fenstermacher JD, Patlak CS (1987) The micro circulation of rat circum ventricular organs and pituitary gland. Brain Res. Bull 18(1): 73-85.

15. Shapiro WR, Hiesiger EM, Cooney AG, Basler GA, Lipschutz LE, et al (1990) " Temporal effects of dexamethasone on blood-to-brain and blood-to-tumor transport of 14C-alpha-aminoisobutyric acid in rat C6 glioma": Journal of Neuro-Oncology 8: 197-204.

16. Frydman-Marom A, Rechter M, Shefler I, Bram Y, Shalev DE, et al (2009)" Cognitive-Performance Recovery of Alzheimer's Disease Model Mice by Modulation of Early Soluble Amyloidal Assemblies": Angew. Chem. Int. Ed 48(11): 1981 -1986.

17. Susanne Aileen Funke and Dieter Willbold (2012)" Peptides for Therapy and Diagnosis of Alzheimer's Disease": Current Pharmaceutical Design 18(6): 755-767.

18. Nau R, rgel FS, Eiffert H (2010) "Penetration of Drugs through the Blood-Cerebrospinal Fluid/Blood-Brain Barrier for Treatment of Central Nervous System Infections": Clinical Microbiology Reviews 23(4): 858–883.

19. Haes AJ, Chang L, Klein WL, Van Duyne RP, (2005) "Detection of a Biomarker for Alzheimer's Disease from Synthetic and Clinical Samples Using a Nanoscale Optical Biosensor": J. Am. Chem. Soc 127: 2264-2271.

20. Larbanoix L, Burtea C, Laurent S, Leuven FV, Toubeau G, et al (2010) "Potential amyloid plaque-specific peptides for the diagnosis of Alzheimer's disease". Neurobiol Aging 31(10): 1679-89.

21. Shawinigan S, Silvius JR (1995) "Doubly lipid-modified protein sequences exhibit long-lived anchorage to lipid bilayer membranes". Biochemistry 34(11)**:** 3813–3822.