P4-272 ALZEIMER'S DISEASE IS AN ENERGY PROBLEM NOT A BIOMASS TROUBLE

Arturo Solis-Herrera, Ruth Isabel Solis Arias, Paola Eugenia Solis Arias, Martha Patricia Solis Arias, *Human Photosynthesis Study Center, Aguascalientes, Mexico.*

Background: The past 30 years have been showed that Alzheimer's disease cannot be cured meanwhile we are trying to fmd the explanationofthe pathophysiologyof the disease merely in the histologic alterations, however, we should think about the role of energy in the neuron physiology. The discovery ofhumanphotosynthesis or the hitherto unknown capacity of eukaryotic cell to dissociate the water molecule break the paradigm; the main source ofenergy of neuron it's not ATP instead is the water of the ventricles and subarachnoid space. Methods: It that the melanin content is very important because melanin is the equivalent to the chlorophyll but in humans, in other words; both substances split the water molecule. Our capacity to dissociate water begin to lose at 26 years old, app. 10% each decade and after fifties goes into free fall. Pharmacologic modulation ofhuman photosynthesis gives astonishing results in patient with Alzheimer's disease. In average in 15 days the patients do not use diapers anymore. Results: The enhancement ofhuman photosynthesis by pharmacologic methods intensifies the water molecule splitting with consequent release of Hydrogen, the main carrier ofenergy in nature and oxygen; diatomic boths. But Oxygen is toxic at any level; so the real value is in Hydrogen. We will show results ofseveral patients treated with our therapy with amazing recovery, may be 80 % oftheir faculties . Conclusions: At light ofhuman photosynthesis, morphologic alterations of cerebral cortex are not due to complex molecules that are pathologically stored, instead is a generalized energy failure; because the biochemical processes that drives neuron physiology are impaired in chaoticway, because in the cerebral cortex, as in other tissue the first requirement for any reaction is energy. ATP cannot be the main source of energy, it's not enough. The astonishing results ofour treatment are consistent, the improve of the AD patients are in several fields ofthe mind, not only in memory; in example the patient regain the self care in an average time of 3 to 6 months.

P4-273 MULTI-FACTORIAL DISEASES REQUIRE MULTI-FACTORIAL THERAPY: WHY NEGLECT PROCAINE IN NEURODEGENERATIVE DISEASES?

Ileana Turcu, Spiru Luiza, *Ana Aslan International Academy of Aging, Bucharest, Romania.*

Background: The multifactorial etiology of neurodegenerative diseases should require drugs able to synergistically target the vulnerability to develop the illness (ultimately, the abnormal expression of responsible genes), and to counteract the effects of those environmental factors able to trigger their onset. **Methods:** Our latest research outcomes regarding the multifactorial pharmacodynamic potential of procaine, as well as recent findings available in the literature, enable us to plead for Procaine as a valuable candidate molecule for future developments in neurodegenerative therapies. **Results:** The "procainome" that we deciphered in pharmacokinetic studies with double-labeled (99mTc and 131-I) procaine suggests that the feed-sideward interactions between the byproducts issued from *in vivo* procaine's hydrolysis cascade may explain the multifactorial pharmacodynamic potential of this molecule. Preclinical pharmacodynamic studies were able to additionally support this potential. The recently demonstrated epigenetic-drug qualities of this molecule (by the Spanish school of oncology) and the demonstration of its capacity of modulating the adrenals' response to stress are also valuable add-ons. **Conclusions:** Thorough research is needed to validate these new insights. As a matter of course, they may reveal surprising therapeutic applications in many neurodegenerative diseases.

P4-274 TOWARDS A MODEL OF SPORADIC ALZHEIMER'S DISEASE: AIDING DESIGN OF SMALL MOLECULE TRKA AGONISTS

Judy Watson[1], Deborah Shoemark[1], Jennifer Hemmings[1], Susan Tyler[1], Mark Fahey[1], Christopher Williams[1], Christopher Bailey[1], Craig McArdle[1], Christopher Caunt[2], David Jane[3], Richard Sessions[1], Matthew Crump[1], Christine Willis[1], Shelley Allen[1], *[1]University of Bristol, Bristol, United Kingdom; [2]University of Bath, Bath, United Kingdom; [3]Univeristy of Bristol, Bristol, United Kingdom.*

Background: Cholinergic basal forebrain neurons, important in memory formation, require nerve growth factor (NGF) for their continued maintenance and are vulnerable in Alzheimer's disease (AD). Application of NGF, through its interaction with tyrosine kinase receptor A (TrkA), has proven beneficial in both AD patients and animal models of AD. Levels of the NGF precursor protein proNGF are increased early in AD brain. Since proNGF has been shown capable of inducing apoptosis, via the p75NTR neurotrophin receptor and its co-receptor sortilin, it has been suggested that this may constitute an important factor in AD pathology. Objectives: Our aims were twofold; to produce small molecule agonists at TrkA and to use proNGF to generate a cell model of sporadic AD in which to test these. **Methods:** Small molecule TrkA binders were identified using *in silico* screening; and structural activity relationships determined using data collected from radioligand binding and agonist/antagonist assays in HEK cells over-expressing TrkA. Nuclear magnetic resonance (NMR) was used to confirm small molecule binding at TrkA. Non-cleavable proNGF (proNGF-nc) was added to PC12 cells, which were characterized for downstream responses including stimulation of intracellular signaling pathways (ERK and AKT), cell viability, neuritogenesis and caspase activation. **Results:** We have identified a compound which displaces NGF with an IC_{50} of 3 ÂµM and can activate ERK in HEK-TrkA cells. It also binds to the isolated NGF-binding domain of TrkA (TrkAd5). PC12 cells express TrkA, p75NTR and sortilin and differentiate in response to NGF, as do cholinergic neurons. Contrary to expected outcomes, we demonstrate here that although less potent than NGF, proNGF-nc acted as a low affinity, but full agonist at TrkA. Moreover, at high concentrations proNGF-nc had equivalent efficacy to NGF. We show that blocking sortilin did not affect assay outcome. Similar results were obtained with differentiated PC12 cells. **Conclusions:** We have produced a potential lead compound towards generation of a small molecule therapeutic for AD. Our results also suggest that an increase in proNGF alone may not be sufficient to induce the AD pathological process, and that other concurrent changes may be necessary.

P4-275 BASELINE COGNITION AND EDUCATION LEVEL AS PREDICTORS FOR RESPONSE TO ACETYLCHOLINESTERASE INHIBITOR IN ALZHEIMER'S DISEASE

Pei-Hsuan Weng[1], Jen-Hau Chen[2], Shih-Yuan Chen[3], Hua-Hsiang Chen[3], Ta-Fu Chen[4], Yu Sun[5], Ping-Keung Yip[6], Li-Li Wen[6], Yi-Min Chu[7], Yen-Ching Chen[3], *[1]Department of Family Medicine, Taiwan Adventist Hospital, Taipei, Taiwan; [2]Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan; [3]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [4]Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; [5]Department of Neurology, En Chu Kong Hospital, New Taipei City, Taiwan; [6]Department of Laboratory Medicine, En Chu Kong Hospital, New Taipei City, Taiwan; [7]Department of Laboratory Medicine, Cardinal Tien's Hospital, New Taipei City, Taiwan.*