AD/PD 2013
The 11th International Conference on Alzheimer's and Parkinson's Diseases
Florence, Italy, March 6-10, 2013

Theme: A Alzheimer's Disease (AD) & Prodromal AD

Topic: 3 Pathophysiology & Disease Mechanisms

Subtopic: 3.c synapse pathology

Title: Thiamine and thiazole binding proteome includes DJ-1, amyloid beta and several membrane proteins

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Text: **Objectives:** Thiamine (vitamin B1) administration causes a transient improvement in cognitive function of some AD patients, with levels of thiamine diphosphate (ThDP) decreased in post-mortem cortex of patients with AD and fronto-temporal dementia. Apart from ThDP acting as coenzyme of central metabolism, thiamine participates in the acetylcholine release. The latter function is suggested to involve unidentified proteins of synaptosomal plasmatic membrane hydrolysing the non-coenzyme derivative thiamine triphosphate (ThTP). This work aims at identification of proteins mediating the non-coenzyme function of thiamine.

Methods: Solubilized proteins of the acetone-delipidated fraction of the crude rat synaptosomes were applied to sorbents with thiamine or thiazole (the thiamine-specific ring) attached. Non-bound proteins were washed out. The ThTP hydrolysing activity (ThTPase) was eluted step-wise by 0.1 M NaCl and 2 M urea. Proteins in the eluates were separated by SDS electrophoresis and identified by mass-spectrometry after trypsin digestion.

Results: The neurodegeneration-related proteins DJ-1 (PARK7_RAT) and amyloid beta (A4_RAT) were identified among those tightly bound to the thiamine/thiazole sorbents. Relative abundance in the eluates of the membrane proteins myristoylated alanine-rich C-kinase substrate (MARCS_RAT), V-type proton ATPase (VATA and VATB), hyaluronan and proteoglycan link protein 1 (HPLN1_RAT) and Thy-1 membrane glycoprotein (THY1_RAT) suggests them as plausible candidates to possess the ThTPase activity or mediate the ThTPase interaction with synaptosomal plasmatic membrane.

Conclusions: Identification of the thiamine/thiazole binding to DJ-1, amyloid beta and several membrane proteins supports pathophysiological significance of thiamine in neurodegenerative diseases beyond the ThDP-dependent enzymes, promoting studies of molecular mechanisms of non-coenzyme function of thiamine.

Author Keywords: thiamine-binding proteins, thiamine in neurodegenerative diseases, thiamine in acetylcholine release