synuclein (α-syn) induced neurodegeneration. **Methods:** Here we assessed the neuroprotective role of RSV in SK-N-BE, a neuroblastoma cell line that we challenged with oxidative stress, a common feature of neurodegenerative disorders. Cells were exposed to 75 μM hydrogen peroxyde (H_20_2) or 75 μM 6-hydroxydopamine (6-OHDA) for 24 h, while sirtuins activity was increased by 7.5 μM RSV addition. Moreover, cells were exposed to 10 μM Aβ (1-42) and 3 μM α-synuclein to trigger toxicity. Finally SIRT1 expression was downregulated by siRNA methodology and sirtuins activity was blocked by sirtinol. **Results:** We found that RSV was able to prevent cellular death triggered by hydrogen peroxyde and the dopaminergic-selecive toxin 6-hydroxydopamine (6-OHDA). This action was independent from RSV antioxidant properties but was likely mediated by Sirt1 activation, as RSV protection was lost in presence of the Sirt1 inhibitor sirtinol and when SIRT1 expression was downregulated by siRNA approach. Moreover, we have confirmed that RSV was alsoable to prevent cellular damage due to the exposure to aggregation-prone proteins as amyloid β-peptide (1-42) (Aβ42) and a mutated form of α-synuclein [α-syn(A30P), exogenously added to cells by means of the fusion protein TAT-α-syn(A30P)]. RSV protection against TAT-α-syn toxicity was likely mediated by sirtuins activation, as it was prevented by sirtinol addition; however, sirtinol was not able to prevent RSV-mediated protection against Aβ(1-42). **Conclusions:** Our data suggest that RSV might be a useful tool in preventing neurodegenerative processes triggered by oxidative stress or protein aggregation.

P4-181 HOMOCYSTEINE, S-ADENOSYLMETHIONINE/S-ADENOSYLHOMOCYSTEINE RATIO, GLUTATHIONE AND NITRIC OXIDE LEVELS IN TGCRDND8 MICE FED WITH B VITAMIN–DEFICIENT DIET

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Background: Increasing evidence indicates that oxidative and nitrosative stress, impaired glutathione (GSH) and homocysteine (Hcy) metabolism can interact in a vicious cycle, which is central to AD pathogenesis. Synthesis of GSH is regulated by cysteine, which is synthesized from Hcy via the transsulfuration pathway. Deficiencies of folate, vitamins B12 and B6 are important for S-adenosylmethionine (SAM)/Hcy metabolism alterations, leading to hyperhomocysteinemia and decrease of SAM/SAH ratio, known as "methylation potential" (MP). Nitric oxide (NO) is involved in physiological functions and in pathological processes leading to tissue damage due to its free radical nature. The production of NO is strongly related to Hcy metabolism, through the regulation of ADMA (asymmetric dymethyl arginine) levels. We already showed, in vitro, that SAM administration can regulate PS1 and BACE expression and β-amyloid production, and in vivo that inhibition of methylation reaction by diet induced hyperhomocysteinemia is able to up-regulate PS1 and BACE. Thus, it was intriguing to study the relationships between Hcy, SAM/SAH ratio, GSH/GSSG and NO levels to understand the link between aberration in redox homeostasis and methylation potential in AD models. **Objective(s):** We used transgenic mice that have an accelerated amyloid accumulation since they are a good model to study the metabolic alterations caused by B vitamins deprivations in AD. **Methods:** TgCRND8 mice together with wild type mice were fed with a deprived diet (without folate, vitamin B12 and B6) or with a control diet. Then, they were sacrificed to analyze Hcy, SAM, SAH, GSH and NO in plasma and tissues by Imx, HPLC and colorimetric assay kits. **Results:** The deficient diet lead to a marked hyperhomocysteinemia, to a decrease in SAM/SAH ratio in plasma and brain, to an increase of GSH/GSSG ratio in TgCRND8 brain probably due to the attempt to compensate for the increased oxidative damage resulting from amyloid β. There is also a brain NO decrease in diet B in TgCRND8 mice, while there are no significant differences in plasma. **Conclusions:** Additional experiments with SAM administration in condition of hyperhomocysteinemia are actually in progress, to test the effect of SAM in GSH and NO production, and amyloid production.

P4-182 INHIBITION OF ABCG2 TRANSPORT FUNCTION BY AMYLOID-BETA PEPTIDE AUGMENTS CELLULAR OXIDATIVE STRESS AND INFLAMMATORY GENE EXPRESSION IN CELLS

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Background: Alzheimer 's disease (AD) is characterized by accumulation and deposition of Aβ peptides in brain. Aβ binds heme forming a complex with peroxidase activities that generates increased levels of non-heme iron. Liable iron causes ROS activation, transcription of oxidant dependent genes and increased APP. ABCG2 is a membrane efflux transporter that regulates cellular heme and porphyrin levels. ABCG2 is induced during hypoxic stress as a protective mechanism to regulate toxic levels of cellular porphyrin and protect the brain from toxic substrate accumulation. **Objective:** This study examines the role of ABCG2 in the regulation of Aβ-induced oxidative stress and inflammatory gene expression. **Methods:** ABCG2 was transfected into HEK293 cells followed by drug uptake assays or H_20_2/TBHP treatment in the presence or absence of Aβ. Conditioned media were prepared from human microglia treated with $A\beta_{1\text{-}42/40}$ and applied to immortalized human brain endothelial cells (iHBEC). RNA/protein was isolated from tissues/cells for RT-PCR/Q-PCR and Western blot. Cell toxicity was assessed by PI assay. ROS was assayed using a ROS-oxidized fluorescent substrate measured on a plate reader or imaged by fluorescent microscopy. **Results:** ABCG2 is up-regulated in human AD/CAA brain and in iHBEC exposed to microglial-conditioned media (MCM). Aβ was shown by co-immunoprecipation to bind ABCG2. ABCG2 efflux of rhodamine was impaired in the presence of $A\beta_{1\text{-}40}$. ROS was induced in HEK293 cells by H_2O_2 or TBHP treatment. $A\beta_{1\text{-}40}$ treatment combined with H_2O_2 or TBHP synergistically increased ROS production. ABCG2 expression inhibited H_20_2/TBHP-induced ROS and decreased cell toxicity but did not reduce ROS accumulation induced by Aβ with H_2O_2 or TBHP. Inflammatory gene expression was increased in H_2O_2-or TBHP-treated HEK293 cells and in iHBEC cells treated with MCM. ABCG2 reduced H_2O_2/TBHP-induced expression of inflammatory genes but not in the presence of Aβ. **Conclusions:** These results suggest that ABCG2 plays a protective role during oxidative stress by maintaining possibly heme/porphyrin levels and reducing inflammatory gene response. Aβ inhibits ABCG2 transport function which augments oxidative stress and inflammatory gene expression. Increased amyloid burden causing transport/clearance restriction and oxidative stress combined with the vulnerability of an aging brain may lead to a synergistic progression of Alzheimer's pathology.

P4-183 INCREASED OXIDATIVE STRESS IS AN EARLY PATHOLOGICAL FEATURE IN 3xTg-AD MICE

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the presence of extracellular senile plaques mainly composed of fibrillar amyloid-beta peptide (Aβ), intracellular neurofibrillary tangles (NFT's) consisting of abnormally hyperphosphorylated tau protein and selective synaptic and neuronal loss. Elevated levels of