THE KYNURENINE PATHWAY AS POTENTIAL TARGET FOR NEUROPROTECTION

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Introduction: Alzheimer's disease is associated with cerebral cognitive deficits exhibiting two cardinal hallmarks: accruement of extracellular amyloid plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. No therapies in clinical use are able to effectively impact the disease course and there is a need of new drugs able to simultaneously ameliorate the numerous pathogenic mechanisms involved in the pathology. Several abnormalities have been described regarding the activation of certain steps of the kynurenine pathway of tryptophan metabolism in Alzheimer's disease, thus suggesting that the metabolites of this pathway might be potential therapeutic targets. In this study, we examined cognitive deficits and kynurenine pathway mediators in the plasma and brain of 3xTg-AD mice. These mice express three transgenes (i.e. amyloid precursor protein, presenilin-1, and tau protein) that phenocopy the critical aspects of Alzheimer's disease neuropathology, thus providing a validated animal model of the human pathology. Furthermore, the effects of a chronic treatment with the lipid modulator palmitoylethanolamide were also evaluated.

Materials and methods: 3-month-old 3xTg-AD mice of both sexes were used to measure basal levels of plasma and brain kynurenine pathway metabolites (HPLC analyses) and cognitive performances (novel object recognition test). Furthermore, the effects of a chronic oral treatment (3 months) with palmitoylethanolamide (100 mg/kg added to animal food) on the above parameters were also evaluated.

Results: Compared to non-Tg mice, male 3x-Tg-AD mice displayed alterations of plasma and brain levels of kynurenine pathway metabolites. The chronic oral treatment with palmitoylethanolamide did not modify the alterations of plasma and brain levels of kynurenine pathway metabolites observed in 3x-Tg-AD mice displayed.

Discussion and conclusions: The possible therapeutic relevance of these findings, together with the multiple connections of kynurenine pathway-related alterations in Alzheimer's disease will be discussed.