GLUTAMINYL CYCLASE EXPRESSION IN SUBCORTICAL NUCLEI MAY ACCOUNT FOR PGLU-Aß PATHOLOGY IN ALZHEIMER’S DISEASE

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The enzyme glutaminyl cyclase (QC) is known to catalyze the pyroglutamate (pGlu or pE)-modification of N-terminally truncated Alzheimer’s disease (AD) Aß-peptides in vivo. This modification provides resistance to proteolysis, rapid aggregation and neurotoxicity and can be prevented by QC inhibitors in vitro and in vivo, as shown in transgenic animal models. In mouse brain QC is only expressed by a relatively low proportion of neurons in most neocortical and hippocampal subregions. Here we demonstrate that QC is highly abundant in subcortical brain nuclei severely affected in AD. In particular, QC is expressed by virtually all urocortin-1-positive, but not by cholinergic neurons of the Edinger-Westphal nucleus, by noradrenergic locus coeruleus and by cholinergic nucleus basalis magnocellularis neurons in mouse brain. In human brain, QC is expressed by both, urocortin-1 and cholinergic Edinger-Westphal neurons and by locus coeruleus and nucleus basalis Meynert neurons. In brains from AD patients these neuronal populations displayed intraneuronal pE-Aß immunoreactivity and morphological signs of degeneration as well as extracellular pE-Aß deposits. Adjacent AD brain structures lacking QC expression and brains from control subjects were devoid of such aggregates. Here we demonstrate the distribution of QC expression and pE-Aß formation in subcortical brain regions affected in AD. Our results may explain the high vulnerability of defined subcortical neuronal populations and their central target areas as a consequence of QC expression and pE-Aß formation in AD. We postulate that among multiple mechanisms contributing to the pathogenesis of AD, QC plays an important role in neurodegeneration and pE-Ab plaque pathology.