A BACE VARIANT (BACEdelta7) - LACKING IN PERIPHERAL CELLS OF ALZHEIMER DISEASE PATIENTS - REGULATES ENZYME ACTIVITY THROUGH HETERODIMERIZATION

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Amyloid peptide (Abeta) deposition in the brain parenchyma is an invariant feature of Alzheimer Disease (AD) and appears the main cause in AD pathogenesis. Abeta is formed by cleavage of Amyloid Precursor Protein (APP) initiated by beta- and gamma-secretases which cleave APP respectively at the N- and C-termini of Abeta. Beta-secretase, known as BACE, is a N-glycosylated aspartyl protease, characterized by apparent MW of 55-60 kDa.
Here we report the characterization of a novel variant of BACE in human cortex, platelets and in neuroblastoma cell lines (SH-SY5Y). Western Blot with BACE antibodies –raised against N- and C-terminal domains of the protein- showed the presence of two specific bands at 57 and 36 kDa, the upper being fully mature, and the lower one not glycosylated, as suggested by incubation with N-glycosidase F. These two proteins are capable of heterodimerize. The complex migrates at 92 kDa. When platelets obtained from control and AD patients were probed with BACE antibodies, a significantly reduction of 36 kDa BACE band in AD platelets compared to controls was obtained. Furthermore, RT-PCR experiments using primers designed for mapping all BACE gene performed in human cortex and platelets, showed the presence, besides the expected transcript of BACE, of a novel splicing form of BACE lacking exon 7 (BACEdelta7). In addition, when in SH-SY5Y cells the down regulation of BACEdelta7 was induced by a NMDA pulse, Abeta production was significantly increased. These findings suggest that a novel splicing form of BACE, identified in human platelets and cortex might play a role on the regulation of BACE activity and AD pathogenesis.