Karolinska Institutet

Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Age dependent β-amyloid isoforms and implications of different drug treatments as studied in different transgenic mouse models and cell lines

AKADEMISK AVHANDLING
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av
Tamanna Mustafiz, MD

Huvudhandledare:
Professor Agneta Nordberg
Karolinska Institutet,
Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Bihandledare:
Med. Dr. Christina Unger Lithner
Karolinska Institutet,
Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Fakultetsopponent:
Professor Kerstin Iverfeldt
Stockholm University,
Institutionen för Neurokemi,
Stockholm, Sverige

Betygsnämnd:
Docent Lena Bergström
Uppsala universitet,
Institutionen för Farmaceutisk Biovetenskap

Docent Oskar Hansson
Lunds universitet,
Institutionen för Kliniska Vetenskaper,
Enheten för Klinisk Minnesforskning

Docent Helena Karlström
Karolinska Institutet,
Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

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ABSTRACT

The Amyloid-β (Aβ) peptide which is the main component of the brain Aβ plaque has been implicated to be one of the major cause of Alzheimer's disease (AD). During the last decade it has become increasingly evident that soluble, oligomeric forms of Aβ are more toxic to neurons than the plaques and might play an important role in the disease pathogenesis. The aim of this thesis was to investigate the time course of different Aβ isoforms and species and how these forms affects the neuropathological changes seen in AD and how different cholinergic drugs can modulate Aβ and its processing.

A translational approach ranging from transfected human neuroblastoma (SH-SY5Y/APPswe) cells, AD-related transgenic mouse models (APPswe and hAChE-Tg//APPswe) to post-mortem AD brain tissue were used to study how changes of different levels of Aβ influence the brain and related processes.

APPswe transgenic mice showed already at 7-days of age, high levels of soluble form of Aβ, as a sign for that Aβ starts to aggregate from birth. Between 7 to 90-days of age, the major Aβ isoforms in brain were shorter forms than $A\beta_{1-40}$. The levels of $A\beta_{1-40}$ were high and remained fairly constant up to 15- months of age while $A\beta_{1-42}$ showed an age-dependent consistent increase from 7- days up to 15-months of age. High levels of Aβ oligomers but low levels of synaphtophysin were observed in 90-days-old APPswe mice probably due to the toxicity of the oligomers. Low levels of α7 neuronal nicotinic acetylcholine receptors (nAChRs) compared to non-transgenic mice were measured in 7-days-old APPswe mice; while an increased number *N*-methyl-D-aspartate (NMDA) receptors binding sites were found at 21-days of age probably reflecting compensatory mechanisms in response to a high Aβ burden. Epigenetic studies showed increased levels of acetylated (AcH3), and di-methylated (2MeH3) histone H3 at 4-months-old APPswe mice. When Aβ was reduced by a γ-secretase inhibitor, there was a reduction in AcH3 in SH-SY5Y/ APPswe cells. Treatment with nAChR agonists influenced the Aβ levels in hAChE-Tg//APPswe transgenic mice and in SH-SY5Y/ APPswe cells.

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