TAU AMYLOID DEBATE – 2010 (SIMILAR TO THE AMYLOID TOPIC 2011)

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We have to be aware that the amyloid cascade hypotheses behind Alzheimer's disease as well as the TAU theory are only hypotheses and none of these theories behind pathogenesis of the disease has a final proof. We also have to be clear that we see different pathological hallmarks in the brains of AD patients, but we do not know why these hallmarks suddenly appear. So we cannot exclude that our approach to clear the brain from visible pathology is the wrong one because we should have asked the question first what is causing the pathology we see to have a real treatment target. Maybe some of the strong arguments behind the amyloid theory were even pushing drug development for AD more into the wrong direction because nobody discussed that familial forms of AD are exceptions, and there is no proof about a real relationship to the biology of sporadic AD. Many assumptions about the pathogenesis have been based on FAD, even the design of most of the disease models which are used for drug development. Of course the amyloid cascade theory was attractive because it delivered several interesting targets like the gamma and beta secretase, like compounds modulating Abeta production, aggregation inhibitors or finally compounds removing plaques, which includes also immunotherapy. Maybe optimistic interpretation of animal data derived from questionable models, and experiments which were not always performed following good scientific practice raised optimism that simply manipulating APP production metabolism and removal can be a final solution for an efficacious treatment of AD. Unfortunately all drug treatment trials so far do not support tremendous effects of amyloid lowering strategies. For me it is not even a surprise because pathological studies already long ago have never shown a direct correlation between disease severity in terms of cognitive dysfunction and amyloid pathology, so it was not logic to believe that there will be a good correlation between lowering of amyloid pathology and improvement of symptoms. Anyhow we also cannot make a final conclusion about Abeta directed drugs and their usefulness so far because for example the toxicity of the postulated dangerous oligomers have not been directly addressed so far, and we learned also that the intervention after onset of symptoms might be too late because potentially highly toxic Abeta has already done that much destruction that a late rescue of neurons is impossible. Anyhow this is a little bit contradictory if we look to clinical data from relatively long term studies with Abeta lowering strategies like GSMs or anti-aggregation compounds, but still a final conclusion is not possible because all of these compounds had a few considerable weaknesses of target toxicity, low blood brain barrier penetration and others. Therefore I feel we need to wait to get first results from interventions in early AD or from studies even starting in pre-symptomatic stage. On the other hand around there have been very little attempts to address the second hallmark of the disease the neurofibrillary pathology. Here we have at least a stronger correlation with cognitive deficits, but the weakness that practically no well designed studies have been performed so far. The Rember trial indicated clinical usefulness of inhibiting TAU aggregation, but the study design has also considerable weaknesses so that a conclusion about real usefulness needs further clinical studies. Other trials targeting TAU protein are in early stage and usually not powered for showing efficacy.

Therefore I would conclude that we should carefully investigate further Abeta directed therapies, but we should at the same time pay more attention towards other drug targets including neurofibrillary pathology. Of course further research to clarify etiopathogenesis of AD is needed to find the real target for treatment of familial AD.