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MEMOSAD

Memory Loss in Alzheimer Disease: Underlying Mechanisms and Therapeutic Targets

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OBJECTIVES: The project was structured in four scientific work packages (WP). WP1 and WP2 focused, respectively, on the characterization of the Abeta and tau assemblies that disrupt signalling pathways essential for synaptic plasticity and memory, and on the identification of those pathways. WP3 addressed the mechanistic link between Abeta and tau, while WP4 finally focused on target validation and the pre-clinical evaluation of Abeta- and tau-anti-aggregation therapeutic strategies.
Insoluble aggregates of Abeta and tau provide the pathological hallmarks of Alzheimer's disease (AD) and the two proteins act in combination to cause synaptic misfunction, memory loss and finally neuronal death. However, the molecular mechanisms underlying these effects are not completely understood. Therefore, MEMOSAD aimed at defining the molecular mechanisms of Abeta- and tau-induced synaptotoxicity and at developing disease-modifying therapeutics for the prevention of memory loss in AD. The specific objectives were: (1) to define precisely the toxic Abeta and tau species responsible for memory loss in AD, (2) to elucidate the mechanisms of Abeta- and tau-mediated toxicity that are at the basis of memory loss, (3) to define the mechanistic link between Abeta and tau that brings about memory loss, and (4) to translate the biological findings into effective, disease-modifying therapeutic strategies.

RESEARCH AND RESULTS
In WP1 we characterized Abeta preparations of various origins, identified the effect of these well-defined Abeta preparations on synapses and memory, and characterized the signalling pathways underlying Abeta-induced toxicity. We generated in vitro amyloid fibrils using 'synthetic' Abeta40 and Abeta42 peptides and demonstrated that for toxicity the quality (40 to 42 ratio) is more relevant than the absolute quantity of peptide. Indeed, in AD the Abeta40/42 ratio changes from 9:1 (physiologic) to ~7:3. We showed that Abeta at pathologic Abeta40/42 7:3 ratio, contrary to physiologic (9:1) ratio: (i) forms fibrils in vitro with a longer 'oligomeric' phase, (ii) affects synaptic function of neurons grown on microchips, (iii) suppresses long-term potentiation (LTP) in brain slices, and (iv) prevents memory formation when injected into rat brain. Thus, Abeta species that are quantitatively similar but qualitatively different can have very different effects on neurons in vivo. We also characterized Abeta from post-mortem human brains. Interestingly, we identified phosphorylation of Abeta monomers and dimers in human AD brains that opens up novel avenues to investigate its role in AD. We also showed a very interesting correlation between soluble Abeta monomer and SDS-stable Abeta dimer and Braak staging, suggesting that these two Abeta species are linked to aberrant tau metabolism. When injected in brain of naïve rats, brain-Abeta preparations prevented memory consolidation and decreased by ~40% synaptic density in the hippocampal dentate gyrus (brain region important for memory and largely affected in AD). The effect on synapses was further analysed in vitro using synthetic Abeta

preparations. At Abeta40/42 ratios of 7:3 Abeta mainly co-localized with synaptophysin (synaptic marker), while such staining was not observed at 9:1 and 10:0 ratios. Extensive washing of neurons did not modify the staining and did not restore synaptic activity for several hours, indicating the rather irreversible nature of the binding. The effect of Abeta on LTP was also demonstrated with brain-derived Abeta. Abeta-injection, but not injection of non-AD brain extract, strongly inhibited LTP. It was recently shown that prion protein (PrPC) is required for plasticity impairment mediated by Abeta assemblies. We thus tested pre-injection of an antibody against PrPC 96-104 (putative Abeta-binding region). The inhibition of LTP by the human brain extract was fully abrogated. Finally, we used APP J9 mice [Hsia AY et al., 1999. Proc Natl Acad Sci USA 96(6):3228-33] to gain knowledge on signalling pathways affected by Abeta. Memory deficits in these mice start at 6 months of age, coinciding with Abeta accumulation and prior to plaques formation. Memory deficits in APP J9 transgenic mice are associated with a specific decrease of CREB target genes related to synaptic plasticity and memory. This decrease is detected at 6- but not at 2-months. Extensive analysis of APP J9 mice-derived neurons indicates that Abeta affects the dephosphorylation (and thus activation) of the CREB transcriptional co-activator CRTC1 (also called TORC1) but not CREB phosphorylation. Thus, deficient CRTC1 dephosphorylation as a result of Abeta accumulation causes CREB-dependent transcriptional deficits and memory deficits.

In WP2 we investigated the effect of expressing tau variants in various models: neuronal cells, brain slices, zebrafish, C. elegans and mice. We used an inducible cell model of tau pathology (N2A cells) to study tau aggregation, degradation and the generation of tau toxicity. We demonstrated that the proteolysis of tau plays an important role in tau aggregation and toxicity. Indeed, tau proteolysis may generate amyloidogenic tau fragments that initiate the aggregation. Enhanced aggregation leads to enhanced toxicity. Autophagy was identified as an important contributor to tau degradation. We also investigated tau toxicity in zebrafish. Tau-transgenic zebrafish recapitulate key pathological features of AD including tau phosphorylation and aggregation, cell death and behavioural disturbances. Axonal transport of mitochondria is greatly reduced in these animals and can be rescued by co-expression of MARK, suggesting that microtubule binding by tau is necessary for transport inhibition. Inhibition of mitochondria axonal transport by mutant tau was also observed in a transgenic C. elegans model of tauopathy. Mitochondria accumulated in the proximal part of the axons in these worms. The zebrafish and C. elegans data support a model that tau-induced pathogenesis is at least partially caused by axonal transport defects. Too, we characterized tau transgenic mouse lines available in the consortium. Thy-tau22 mice [Schindowski K et al., 2006. Am J Pathol 169(2):599-616] display tau pathology in the absence of motor dysfunction. Long-term potentiation and depression (LTP and LTD) as well as memory formation are affected in these mice. These mice present in addition non-cognitive neuropsychiatric disorders characteristic of AD. Various tau transgenic lines in which expression of tau can be switched on and off [Eckermann K et al., 2007. J Biol Chem 282(43):31755-65/Mocanu MM et al., 2008. J Neurosci 28(3):737-48] were characterized. Tau 'pro-aggregation' mice display impairments in hippocampus-dependent behaviour as well as hippocampal LTP and these deficits are reversed by switching off the expression of the tau transgene. Histopathologically, during the tau expression phase the hyperphosphorylation and aggregation of tau is accompanied by a loss of neurons and synapses. Almost no pathology is observed in anti-aggregation mice. When the expression of tau is discontinued, there is no visible recovery of tau aggregation and neuronal loss, however, there is partial recovery of synapses, what may explain the recovery of LTP. Interestingly, the remaining tau aggregates in switched-off mice consist of endogenous mouse tau whereas the human tau is no longer visible. This suggests that the tau aggregates are in a dynamic equilibrium with their subunits and that normal tau can form aggregates if "poisoned".

In WP3 we studied the synergy between Abeta and tau and its consequences on neuronal and synaptic damage and on memory loss. We also investigated the relevance of tau in the Abeta-induced damage.
We showed that toxic Abeta oligomers added to cultures of WT hippocampal neurons cause a disruption of the axonal sorting machinery and a redistribution of endogenous tau into soma and dendrites. Tau redistribution is one of the earliest signs of neuronal degeneration in AD. Missorting affects not only tau, but also other axonal markers such as neurofilaments, and correlates with a dramatic local decrease of microtubules. In the missorted dendritic regions there was a depletion of spines and spine-related proteins. Thus Abeta oligomers evoke responses that disrupt the axonal sorting machinery; they allow endogenous tau to enter dendrites and to destroy spines and microtubules locally. This is in analogy to the loss of spines and microtubules observed in AD. Abeta oligomers also seem to induce tau kinases specific for the KXGS motifs in tau repeats (MARK, p70S6K, BRSK/SADK), the consequent tau phosphorylation and dissociation from microtubules. By contrast, most proline-directed kinases tested (MAPK, JNK, GSK3b, but not cdk5), all considered to be involved in the pathological phosphorylation of tau in AD, showed little change upon Abeta treatment. Interestingly, Abeta preparations with toxic Abeta40/Abeta42 ratio (7:3) are ~10 times more potent in inducing tau-related changes than an ADDL preparation (contains monomers, dimers, trimers and some high molecular weight aggregates).

And only 'mild' effects were observed with Abeta dimer preparations. Finally, other cell stressors such as oxidative stress, serum deprivation, excitotoxicity and extracellular ATP, caused a similar effect as the Abeta oligomers treatment, namely tau missorting, local disappearance of spines and microtubules, and increased tau phosphorylation. Thus, missorting of tau seems to be a general response of neurons to diverse types of stress, one of them being the Abeta oligomers. We performed a similar analysis of Abeta-induced changes using neurons derived from tau knock-out mice. There was a notable difference in the response of neurons to Abeta and other cell stressors. Tau KO neurons were less inhibited by Abeta with regard to spontaneous activity, they were less affected in terms of loss of dendritic microtubules or missorting of neurofilaments, even though Abeta oligomers were similarly directed to bind to synapses. A major difference was that the loss of spines was less pronounced, arguing that tau plays a role in the Abeta-induced synaptic loss. We next analysed the effect of Abeta preparations on synapses in vitro (MEA chip assay) and the relevance of tau in the Abeta-mediated toxic effects. WT and tau KO hippocampal neurons were grown at the same cell density on microchips and the rate of neural firing was compared before and after addition of Abeta preparations with different Abeta42/40 ratios. Overall, tau KO networks were ~50% less susceptible to Abeta42/40 10:0 and 3:7 inhibitory effects than the WT cultures, and were not sensitive to Abeta42/40 0:10 and 1:9, similar to WT neurons. Altogether, we revealed a mechanism of Abeta toxicity in neurons and demonstrated the relevance of tau as a mediator of Abeta-induced toxicity.

WP4 focused on four topics: (i) validation of candidate therapeutic targets, and the pre-clinical evaluation of novel therapeutic strategies, (ii) Abeta anti-aggregation, (iii) tau-anti-aggregation, (iv) tau immunotherapy. A number of candidate therapeutic targets were identified in the consortium including: autophagy as main system for degradation of tau (N2A cells); de-ubiquitinases as contributors to tau toxicity (C. elegans); decrease levels of the CREB co-activator CRTC1 as mediator of the Abeta-induced memory deficits (neurons from APP J9 transgenic mice); and cholesterol-modifying enzymes whose levels change in tau-transgenic mice (Thy-tau22) upon voluntary exercise and concomitant with memory improvements. We validated these candidate targets as follows: autophagy enhancers (like trehalose) reduced the level of aggregated tau and the concomitant tau toxicity in the N2A cell model; down-regulation of the de-ubiquitinase CYLD-1 in worms improved the tau-associated defects; adenoviral-mediated gene transfer of CRTC1 in the hippocampus of APP J9 mice significantly ameliorated the early learning and memory impairments; and viral-mediated expression of CPY46A1 (encoding an enzyme involved in brain cholesterol efflux) in the hippocampus of Thy-tau22 mice improved memory deficits. In addition, we validated in different models the modulation of tau phosphorylation as a relevant therapeutic treatment in AD. Most notably, treatment of Tau AD mice with selenium (an agonist of the tau phosphatase PP2A) could rescue the behavioural and hippocampal synaptic plasticity defects. Interestingly, Se2+ treatment also improved synaptic plasticity defects of APP/PS1 mice. Thus, the beneficial effect of Se2+ is not only apparent in tau-transgenic but also in a different AD model that do not over-express tau.

We generated in the consortium a number of small molecule (non-peptidic) Abeta anti-aggregation inhibitors. Importantly, oral doses of the compounds improved memory performance in two rodent models: rats upon intra-cerebroventricular injection of Abeta oligomers (acute model) and APP/PS1 double transgenic mouse model. The compounds were also effective in preventing the Abeta-induced decrease in synaptophysin levels in primary neuronal cultures. Interestingly, reduction in synaptophysin levels is a feature of AD that correlates with cognitive decline.
We also generated in the consortium tau anti-aggregation compounds (from the rhodanine class and from the phenylthiazolyl-hydrazide (PTH) class). So far the compounds were validated in a C. elegans model of taupathy. The compounds significantly improved the movement defects and the abnormal changes in neuronal morphology. Pre-clinical validation in mice is pending. Importantly, we validated an alternative strategy targeting tau. Immunization of Thy-tau22 mice against the ser422 tau epitope generated an immune response specific for this epitope, reduced aggregated tau and delayed cognitive deficits. Thus, tau immunotherapy may be a useful therapeutic strategy for AD and other tauopathies.

We had proposed to deliver by the end of the project 3 or 4 validated therapeutic targets and at least 2 compounds with demonstrated therapeutic efficacy in mouse models of AD. Among the targets identified and validated in the consortium the most relevant are: the Aph1B subunit of gamma-secretase; the CREB-co-activator CRTC1 (or TORC1); the tau ser422 epitope; toxic ratios of Abeta40 to Abeta42 (10:0, 7:3); autophagy. We also generated non-peptidic Abeta aggregation inhibitors (like SEN1428 and SEN1500) and demonstrated their beneficial effects on memory tasks in two different murine models (Abeta-injected rats and APP/PS1 transgenic mice). Finally and even if not proposed in the initial Grant Application, we validated tau immunotherapy (against tau ser422) as a useful therapeutic strategy for AD and other tauopathies. Large-scale

drug screening efforts focusing on the validated targets will be done in a follow-up of MEMOSAD, in collaboration with the pharmaceutical industry. The targets identified or other components of the signalling cascades where they participate may have an additional value as biomarkers with a potential use as diagnostic tools.

BENEFITS: The data obtained is also of relevance for other neurodegenerative disorders, notably those involving tauopathy and synaptic loss (e.g., Parkinson's disease, Pick's disease, frontotemporal dementia, etc.). Therefore, the project is expected to have an impact on various societal levels: (i) on the health of European citizens by contributing to an early diagnosis of AD, and the development and validation of new therapies for treatment and prevention of a so far incurable brain disease; (ii) on Europe's economy, if medical treatment can successfully delay symptoms by a few years and, thus, substantially decrease the economic burden of AD - measured as productivity loss by affected individuals and caregivers as well as by the burden on Europe's health care systems; (iii) on Europe's competitiveness and the innovative capacity of its health-related industries by contributing to stop loosing the major role as a global centre for biomedical research, evidenced in the last decades especially in comparison to the US and Japan.

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