2. Aim of the study

While there is thus little debate over the presence of a local inflammatory reaction in AD, considerable controversy remains concerning how immunoregulatory factors and their cellular activities contribute to the pathology and how the actions of microglial cells participate in destructive cascades or cycles. The central aim of this study was, therefore, to evaluate the microglia-activating capacities of Aß preparations, IL-1, IL-18, IL-6 and α2M in single and combined stimulations of mouse microglial cultures. Release of cyto- and chemokines thereby served as a main quantitative parameter of the activation consequence.

How do Aß preparations affect microglial release activity?

Aß1-40 and Aß1-42 appear as two main amyloid species. The peptides are highly complex in terms of their tendency to polymerise and to aggregate into the fibrils. This complicates an identification of the active species required for induction of microglial activity. A prerequisite of this study was to define optimal conditions for Aß peptide preparation in order to obtain a microglial release response.

Do AD-associated cytokines act as co-stimulators in the activation of microglia by Aß?

Direct stimulation of microglial cells with Aß peptide is followed by no or barely detectable release of cyto/chemokines and NO. In studies showing cytokine production and release by Aß-stimulated microglia co-stimulation with e.g. LPS was required. However, this co-stimulator is not a relevant factor in AD. Due to the fact that IL-1 is implicated in AD pathology and that a high level of homology in cytoplasmic domain exists between Toll like receptors (TLRs) and IL-1R, IL-1 was considered in a synergistic stimulation context with Aß.

A putative involvement of IL-18, as a new member of IL-1 family and IL-6, which are known to be significantly elevated in AD brains, were also examined.

Does the protease inhibitor a2M contribute to microglial activation and is there a supra-additive effect when combined with Aß?

α2M is an AD-related protease inhibitor and has been implicated in several AD pathophysiological processes. However, little is known about a direct effect of α2M on microglial cells. An aim of this study was to examine effect of microglial activation upon exposure to α2M alone or in combination with Aß peptides.