Peripheral and central biodistribution of (111)In-labeled anti-beta-amyloid autoantibodies in a transgenic mouse model of Alzheimer's disease.

Abstract:
Active as well as passive immunization against beta-amyloid (Abeta) has been proposed as a treatment to lower cerebral amyloid burden and stabilize cognitive decline in Alzheimer's disease (AD). To clarify the mechanism of action underlying passive immunization, the in vivo distribution (and sites of degradation) of peripherally administered radiolabeled human and mouse anti-Abeta antibodies were analyzed in a transgenic mouse model of AD. In APP23 mice, a model in which mutated human amyloid precursor protein is overexpressed, the biodistribution of intravenously applicated (111)indium-conjugated affinity-purified human polyclonal autoantibodies (NAbs-Abeta) was compared to that of monoclonal anti-Abeta(1-17) (6E10), anti-Abeta(17-24) antibodies (4G8) and anti-CD-20 (Rituximab), a non-Abeta targeting control. Blood clearance half-lives were 50+/6h for Rituximab, 20-30h for NAbs-Abeta, 29+/5h for 4G8 and 27+/3h for 6E10. Blood activity was higher for 6E10 at 4h as compared to 4G8, Rituximab and NAbs-Abeta. At the 96h time point, Rituximab had the highest blood activity among the antibodies tested. As expected, all antibodies displayed hepatobiliary clearance. Additionally, NAbs-Abeta was excreted in the urinary tract. Liver and kidney uptake of NAbs-Abeta increased over time and was higher than in the monoclonal
antibodies at 48h/96h. The brain-to-blood radioactivity ratio for NAbs-Abeta at later time points (>48h) was higher than that of 6E10, 4G8 and Rituximab. In addition, the distribution varied, with highest values found in the hippocampus. Our data indicate a cerebral accumulation of human NAbs-Abeta in the APP23 model. Further studies with human immunoglobulins and particularly with those that recognize different Abeta-epitopes are required in order to delineate in more detail the mode of action of NAbs-Abeta.