19 Cholesterol and Alzheimer's disease

High cholesterol levels also promote the onset of Alzheimer's disease – the world's most common form of dementia. In Germany, approx. 900,000 of the nearly 1.5 million dementia sufferers have Alzheimer's, which the WHO cites as contributing to 60–70 % of dementia cases worldwide. Besides non-functioning tau proteins in the neurofibrillary bundles, other causes of Alzheimer's come from depositions (plaques) of amyloid-beta, a peptide of 42 amino acids in length (**Aβ-42**), which is found mainly in the limbic system, neocortex and hippocampus (Bateman et al. 2012). One function of the hippocampus is converting important information from short-term to long-term memory (▶ Chapter 92). The Aβ-42 peptide is formed by cleavage of a membrane-bound amyloid precursor protein in the presence of the enzyme **gamma-secretase**. The gamma-secretase-activating protein increases the activity of gamma-secretase (He et al. 2010), but so does cholesterol – with the result that elevated cholesterol levels are often accompanied by increased **amyloid plaque formation**.

Cleavage of the precursor protein also releases **Aβ-40**, a peptide two amino acids shorter than Aβ-42. This building block plays a positive role in pathogenesis insofar as it throttles **cholesterol biosynthesis** and thus also indirectly reduces the concentration of neurotoxic Aβ-42 by decreasing gamma-secretase activity. When cholesterol levels are normal, both feedback loops are in equilibrium.

When cholesterol levels are high, however, the protective function gained by lowering Aβ-40 cholesterol is often no longer effective enough, and the harmful properties of Aβ-42 predominate. This is even more relevant considering that Aβ-42 activates gamma secretase, thereby promoting further cleavage of the pre-amyloid. Aβ-42 achieves this indirectly by hindering neurons in the brain from forming **sphingomyelin**. In fact, sphingomyelin is capable of inhibiting gamma-secretase by itself. However, it can only limit pre-amyloid cleavage when it is present in sufficient concentrations.

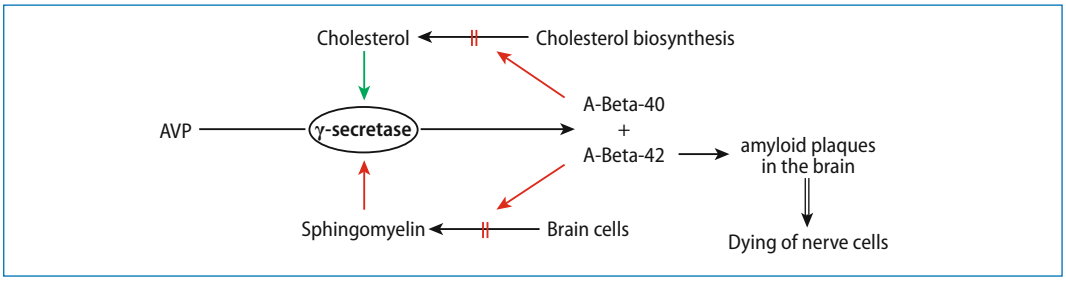

Fig. 19.1 Amyloid plaques formation: *black arrow* formation, *green arrow* activation, *red arrow* inhibition, *APP* amyloid precursor protein, *A-Beta-40* and *-42* APP splice products

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