Histone acetyltransferase (HAT) activators as chromatin remodelers in the treatment of Alzheimer's disease

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Most of the clinical trials against Alzheimer's disease (AD) share the common philosophy of interfering with amyloid-beta and tau levels and/or aggregation. However, in addition to their role in pathology, these proteins have normal physiological roles that might affect efficacy and cause side effects of therapeutic approaches based on this philosophy. This might explain, at least in part, recent failures of Alzheimer clinical trials. In an attempt to discover an approach alternative to drugs interfering with amyloid-beta and tau levels and/or aggregation, wehave found that because of the role of epigenetic mechanisms such ashistone acetylation in memory formation,targeting histone acetylation downstream of amyloid-beta might constitute a viable and effective strategy.In support of such an approach we have discovered that AD patients have a decrease in acetylation of histone lysine residues important for memory. Consistent with these results, amyloid-betareduces acetylation of specific histone lysines that are important for memory formation in mice. We have also found that amyloid-betareduces endogenous expression of CREB binding protein (CBP) and p300/CBP associated factor (PCAF), two histoneacetyltransferases (HATs)that are relevant for memory formation. The main strategy currently used to up-regulate histone acetylation involves histone deacetylase (HDAC) inhibitors. However, the pleiotropic effect of nonspecific HDAC inhibition may hamper their therapeutic potential. HAT activators, in turn, might constitute an alternative avenue to enhance histone acetylation. To this end, we have started a course of investigation involving the design of HAT activators that target specifically memory related HATs downstream ofamyloid-beta. Using a SAR approach, we designed and synthesized a series of compounds that lead to YF2, a novel potent activator of memory related HATs, CBP, p300 and PCAF. YF2 was found to be soluble, membrane permeable and blood-brain barrier permeable. YF2 was also found to rescue the reduction in histone acetylation followingamyloid-betaelevation, and rescue synaptic and memory deficits induced byamyloid-betaexposure. These findings define a new molecular target and a strategy to manipulate this target to the benefit of the patient.