Dihexa is a subset of angiotensin IV-related molecules that are known to possess procognitive/antidementia properties and have been considered as templates for potential therapeutics.

However, this potential has not been realized because of two factors: 1) a lack of blood-brain barrier–penetrant analogs, and 2) the absence of a validated mechanism of action. The pharmacokinetic barrier has recently been overcome with the synthesis of the orally active, blood-brain barrier–permeable analog N-hexanoic-tyrosine-isoleucine-(6) aminohexanoic amide (dihexa).

Clinical studies suggest that Dihexa improves cognitive function as shown in animal models of diseases such as Alzheimer's. Angiotensin IV is a derivative of the vasoconstrictor angiotensin II which has been shown in animal studies to enhance acquisition, consolidation and recall of learning and memory when administered centrally or peripherally. In an assay of neurotrophic activity, Dihexa was found to be seven orders of magnitude more potent than brain-derived neurotrophic factor and is thought may be able to help in the repair of the brain and nerves in neurological disease.

Dihexa binds with high affinity to hepatocyte growth factor (HGF) and both Dihexa and its parent compound Norleucine 1-AngIV (Nle1-AngIV) induce c-Met phosphorylation in the presence of subthreshold concentrations of HGF and augment HGF-dependent cell scattering. Further, Dihexa and Nle1-AngIV induce hippocampal spinogenesis and synaptogenesis similar to HGF itself. These actions were inhibited by an HGF antagonist and a short hairpin RNA directed at c-Met. Most importantly, the procognitive/antidementia capacity of orally delivered dihexa was blocked by an HGF antagonist delivered intracerebroventricularly as measured using the Morris water maze task of spatial learning.

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