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Short Communication

Effectiveness of the tetrapeptide HAEE: an innovative approach to Alzheimer's treatment in experimentation

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Abstract

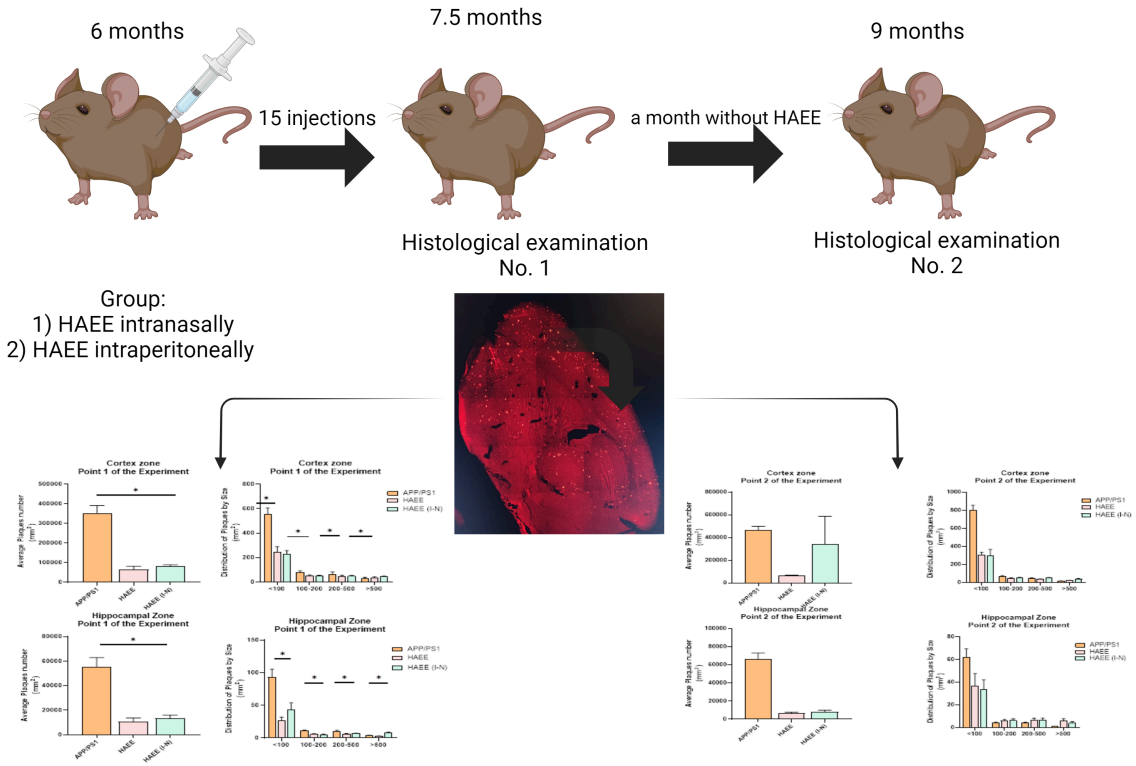
Introduction: Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by a progressive decline in cognitive functions. According to the "Alzheimer's Disease International", there were 36 million reported cases of AD worldwide in 2009, with projections suggesting an increase to 66 million by 2030 and 115 million by 2050.

Materials and Methods: The study was conducted on three experimental groups consisting of male APPswe/PS1dE9/Blg mice on a mixed genetic background with C57Bl6/Chg animals. Each group included 10 mice. At the baseline (point 0), peptides and drugs were administered to two groups of animals aged 6 months. The treatments were given circadianly every 48 hours without breaks for one month. Subsequently, at point 1 of the experiment, half of the group (n=5) was selected for further histological analysis of the brain. The remaining half did not receive any treatments for one month before undergoing histological examination. Statistical significance between experimental and control groups was assessed using an unpaired Student's t-test at $p<0.05$.

Results and Discussion: Histological analysis indicated the efficacy of the tetrapeptide HAEE at a dosage of 50 mg per kg of mouse weight, showing a significant reduction in amyloid plaques in the cerebral cortex and hippocampus of the mice.

Conclusion: The study supports the proposed hypotheses and suggests further investigation into additional drug groups recommended for Alzheimer's treatment for comparative studies.

Graphical abstract



Keywords

tetrapeptide, Alzheimer's disease, HAEE, treatment, APP/PSEN1

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative pathology, characterized by a progressive decline in cognitive functions. According to the "Alzheimer's Disease International", there were 36 million reported cases of AD worldwide in 2009, and it is projected that this number will increase to 66 million by 2030 and to 115 million by 2050. Hereditary forms of the disease account for less than 1% of all cases and are associated with mutations in genes that lead to increased levels of beta-amyloid (Aβ). According to the amyloid hypothesis, the accumulation of Aβ in the form of amyloid plaques is a key mechanism in the pathogenesis of AD. Anti-amyloid therapy aimed at inhibiting Aβ aggregation is considered a promising treatment strategy. The synthetic peptide HAEE has demonstrated significant efficacy in slowing cerebral amyloidogenesis in transgenic mice, outperforming other drugs such as Alzhemed (Lysikova et al. 2023).

Aim: to evaluate the effectiveness of intraperitoneal and intranasal administration of the tetrapeptide HAEE in APPswe/PS1dE9/Blg mice through histological analysis of amyloid plaques.

Materials and Methods

Investigated compound

The composition represents an effective delivery of the tetrapeptide [Acetyl]-His-Ala-Glu-Glu-[Amide] (HAEE), used as an active pharmaceutical ingredient, across the blood-brain barrier (BBB) for the treatment of neurodegenerative diseases, including Alzheimer's type dementia. The pharmaceutical composition for treating neurodegenerative diseases contains an effective amount of HAEE peptide in an equimolar complex HAEE-Zn-HSA with zinc and human serum albumin.

Animals

The study was conducted on three experimental groups consisting of male APPswe/PS1dE9/Blg mice on a mixed genetic background with C57Bl6/Chg animals. Each group included 10 mice.

Study design

Peptides and drugs were administered to two groups of animals aged 6 months. In the first group, the drug was administered intraperitoneally – tetrapeptide HAEE at a

dosage of 50 mg per kg of mouse weight. In the second group, the drug was administered intranasally at the same dosage. The third group served as a control group of transgenic animals (negative control). The drugs were administered circadianly every 48 hours during 1,5 months; subsequently, at point 1 of the experiment, half of the group (n=5) was selected for further histological analysis of the brain. The remaining half did not receive any treatments for one month before undergoing histological examination (Fig. 1).

Statistical analysis

Statistical processing was performed using GraphPad Prism Software 8.0 (GraphPad Software Inc, USA). Normality testing was conducted using the Shapiro-Wilk test. For post hoc analysis, an unpaired Student's t-test or Mann-Whitney test was used. Results were considered significant at $p \leq 0.05$.

Results and Discussion

Comparison of plaque counts in APPswe/PS1dE9/Blg mice aged 7.5 months following intraperitoneal and intranasal administration of HAEE

Data characterizing the average number of plaques and their size distribution are presented in Figure 2.

The graph shows the total area covered by plaques and their distribution by size (mm²). The APP/PS1 group showed an average surface area value of 367 thousand mm² in the cortex and 56 thousand mm² in the hippocampal zone. The HAEE and HAEE (I-N) groups showed results of 63.3 thousand mm² and 84.3 thousand mm² in the cortex; 12 thousand mm² and 16 thousand mm² in the hippocampus, respectively. Thus, we observe a significant increase in therapy effectiveness using HAEE compared to the control group with the disease.

Comparison of plaque counts in APPswe/PS1dE9/Blg mice aged 9 months following intraperitoneal and intranasal administration of HAEE

Data characterizing the average number of plaques and their size distribution are presented in Figure 3.

The graph shows the total area covered by plaques and their distribution by size (mm²). The APP/PS1 group showed an average surface area value of 467 thousand mm² in the cortex and 63 thousand mm² in the hippocampal zone. The HAEE and HAEE (I-N) groups showed results of 63.3 thousand mm² and 372 thousand mm² in the cortex; 6 thousand mm² and 8 thousand mm² in the hippocampus, respectively. We can note trends towards an increase in plaque counts in the absence of treatment, preservation of pharmacological effect with intraperitoneal administration of HAEE, and some dispersion of effect with intranasal administration of HAEE (Lysikova et al. 2023).

Discussion

There are numerous approaches worldwide that characterize various aspects of treating neurodegenerative diseases (Polikarpova et al. 2022; Korokin et al. 2023). When discussing tetrapeptide HAEE as an innovative approach to treating Alzheimer's disease (AD), some positive and negative aspects can be highlighted. Positive aspects include effectiveness with both intraperitoneal and intranasal administration. It should be particularly noted that HAEE demonstrates its effectiveness within the context of amyloid hypothesis, which is one of the most studied theories regarding AD pathogenesis.

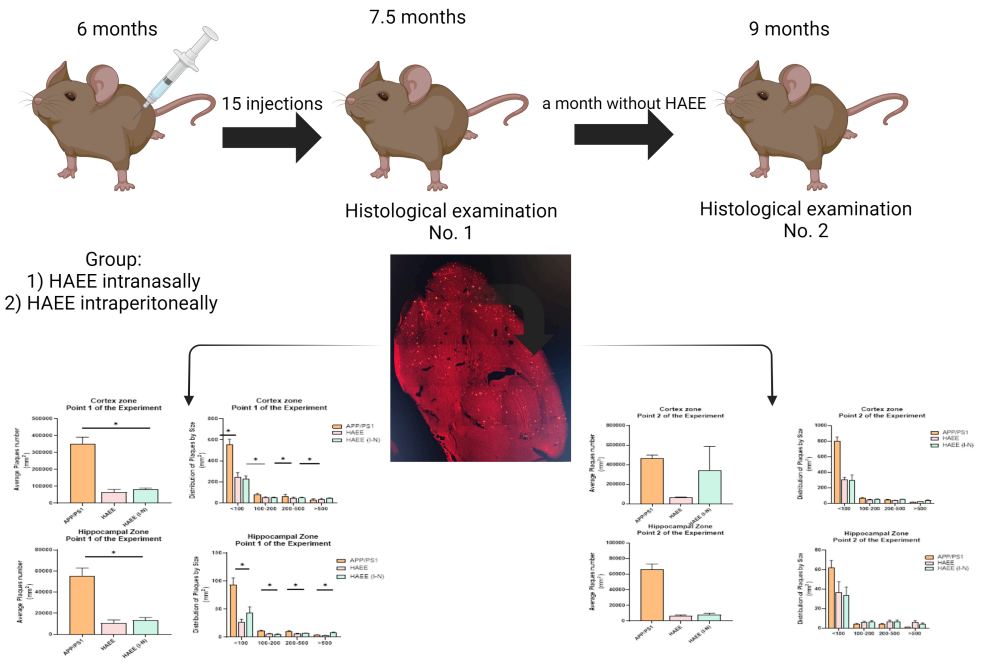


Figure 1. Study design.

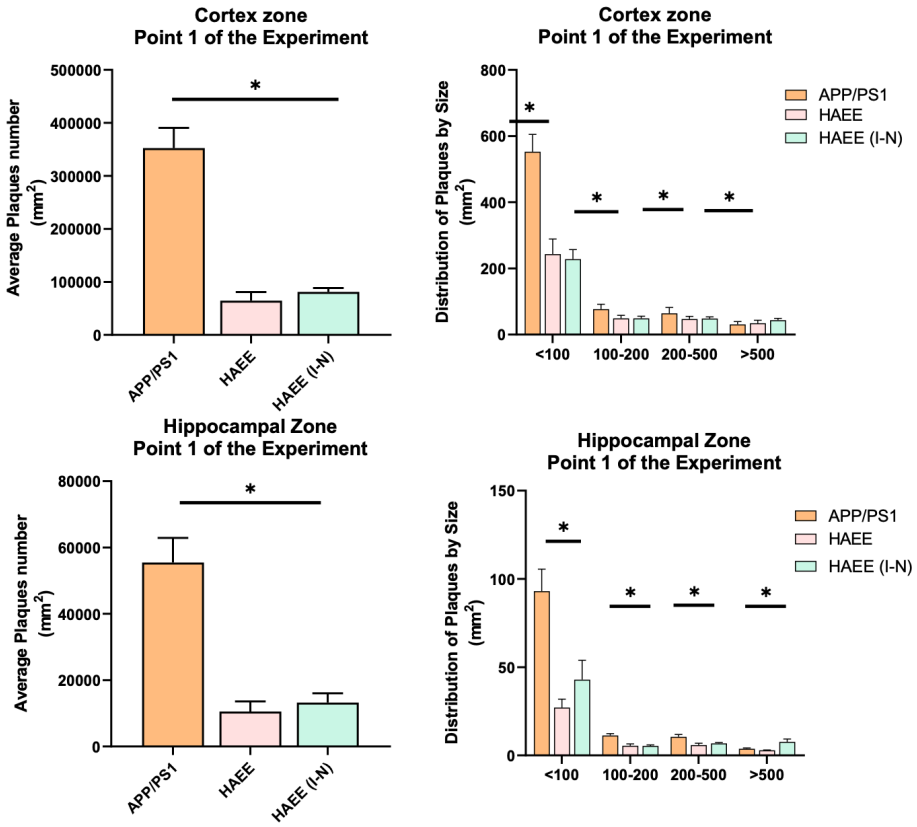


Figure 2. Comparison of plaque counts in APPswe/PS1dE9/Blg mice aged 7.5 months following intraperitoneal and intranasal administration of HAEE. ***Note:*** APP/PS1 – intact mouse group; HAEE – group with intraperitoneal administration of HAEE; HAEE (I-N) – group with intranasal administration of HAEE; * – p≤0.05.

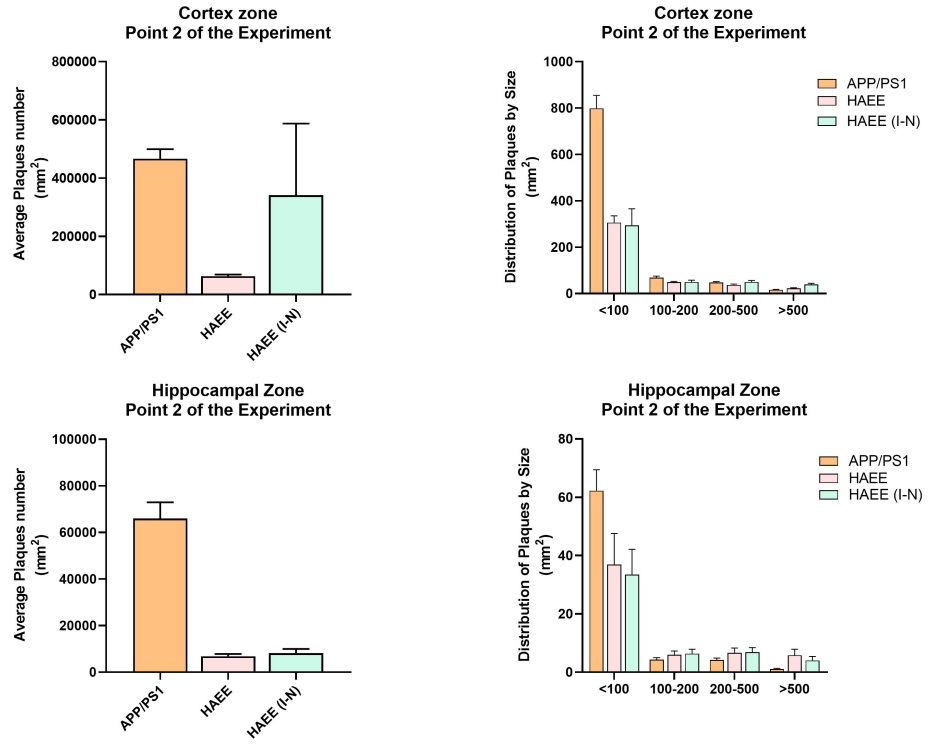


Figure 3. Comparison of plaque counts in APPswe/PS1dE9/Blg mice aged 9 months following intraperitoneal and intranasal administration of HAEE. ***Note:*** APP/PS1 – intact mouse group; HAEE – group with intraperitoneal administration of HAEE; HAEE (I-N) – group with intranasal administration of HAEE; * – p≤0.05.

Possible downsides to this scientific hypothesis upon further study may include short-term action: short half-life of tetrapeptides in plasma limits their therapeutic effect, requiring frequent administration which may cause inconvenience for patients (Froelich et al. 2019; Bach et al. 2020; Zhang et al. 2021).

Thus, despite promising results from studying tetrapeptide HAEE, it is essential to consider both its advantages and limitations. Success in developing effective treatments for AD will require a comprehensive approach in future research.

Conclusion

The study supports the validity of proposed hypotheses and suggests further investigation into additional drug groups recommended for Alzheimer's treatment for comparative studies. Additionally, further research on biodistribution of HAEE with its intranasal administration is necessary for additional confirmation of obtained results.

Conflict of interest

The authors declare the absence of a conflict of interests.

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Acknowledgments

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Data availability

All of the data that support the findings of this study are available in the main text.

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