ORAL TREATMENT OF MICE WITH POSIPHEN™ SIGNIFICANTLY LOWERS BRAIN LEVELS OF BETA-AMYLOID (1-42)

G Bruinsema1, E Cullen2, NH Greig3, K Sambamurti4, L Friedhofer5, D-M Chen6 and DK Lahn6

1Axonix Inc., New York, NY, USA; 2 Montvale Pharmaceutical Development, Montvale, NJ, USA; 3 Drug Design & Development Section, Intramural Research Program National Institute on Aging, NIH, Baltimore, MD, USA; 4 Department of Physiology & Neuroscience, Medical University of S. Carolina, Charleston, SC, USA; 5 Pharmaceutical Special Products Group, LLC, River Vale, NJ, USA; 6 Department of Psychiatry, Institute of Psychiatric Research, National Institutes of Health, Baltimore, MD, USA.

Abstract

Background: Major hallmarks of Alzheimer’s disease (AD) include synaptic loss, cognitive deficits and abnormal protein deposition, particularly of beta-amyloid (Aβ), which is derived from amyloid precursor protein (APP) by endoproteolytic processing. Aβ1-42 ([Aβ1-42]), one of the APP products formed, is a principal component of the plaques that are found in the brains of AD patients. Current AD therapeutic strategies include improving cognitive processes, primarily through cholinesterase (CHE) inhibition. No therapy that reduces brain Aβ levels is currently available. Our aim has been to study different emerging drugs, such as (-)-phenserine tartrate (PT), a selective acetyl-CHE inhibitor, currently in phase II AD clinical trials, on the Aβ pathology. In a previous study, PT, which improves cognition in rodents and humans due to CHE inhibitory action, lowered APP and Aβ levels by a CHE independent mechanism. Posiphen™([+]-phenserine tartrate) is the positive enantiomer of PT, and has been shown to lower APP levels in human neural cell cultures. The current study examined the effects of orally administered Posiphen™ on Aβ1-42 levels in mouse brain.

Methods: Male C57Bl6/J mice were orally treated either for 7 or 21 days with different doses of Posiphen™ (0 mg/kg (vehicle-control), 4 mg/kg, 20 mg/kg, and 60 mg/kg). On day 7, the mean brain Aβ1-42 levels in the 25, 50 and 75 mg/kg Posiphen groups were significantly lower than in the vehicle control, by 34.7%, 56.9 and 60.2%, respectively. On day 21, the mean brain Aβ1-42 levels in the 25, 50 and 75 mg/kg Posiphen groups were significantly lower than in the vehicle control by 52.3%, 56.9% and 60.2%, respectively. Mean Posiphen plasma concentrations at the time of sample collection were lower than maximum Posiphen plasma concentrations in a recent clinical pharmacology study of Posiphen in healthy men and women.

Results: Posiphen™ administration lowered brain Aβ1-42 levels in mice, and suggest that the therapeutic ratio may also be favorable in humans.

Conclusion: This work was supported by Axonix Inc., New York, NY, USA and the National Institutes of Health, Baltimore, MD, USA.

Acknowledgements

References


Figure 1. Posiphen™([+]-phenserine tartrate)

Figure 2. Mouse brain Aβ1-42 (means±SEM) after 21 days of Posiphen™ treatment administration

Figure 3. Mouse brain Aβ1-42 (means±SEM) after 21 days of Posiphen™ treatment administration

Figure 4. Mean Posiphen plasma concentrations following oral administration in mice and healthy women

Figure 5. Mean Posiphen plasma concentrations following oral administration in mice and healthy women

Significantly different from control determined was Posiphen™ treatment.

Conclusion

In mice, orally administered Posiphen™ lowered brain Aβ1-42 levels at plasma concentrations that are attainable with oral dosing in humans.

References


Presented at the International Conference on Alzheimer’s Disease and Related Disorders, Madrid, Spain, July 15-20, 2006.