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Single voxel spectroscopy on two memory-enhancing drugs proposes glutamate modulation

Statement of the Problem: Alzheimer's disease is the most common form of dementia, affecting up to 70% of all people with dementia. A class of disease-non-modifying drugs, cholinesterase inhibitors is commonly used to treat Alzheimer's disease (AD). These drugs increase glutamatergic transmission and improve memory, however, they do not protect from disease progression and lose efficacy over time. Other approaches such as the inhibition of beta amyloid and tau protein formation have so far failed to improve the symptoms or modify the progression of this disease. We report here on a new class of molecules, choline analogs that improve memory in rodents and non-human primates as well as demonstrated neuro-protection in cellular models. We investigated the effects of these candidates on glutamate release in the hippocampus.

Methodology: Anaesthetized rats were either treated I.V. saline or CB8411 (50 µg/kg) or CB2233 (100 µg/kg). These subjects were then immediately scanned using a 9.4T ultra-high Bruker MRI, a 2.5x4x4 mm voxel in the hippocampus was scanned and glutamate levels were determined to determine baseline levels. After 30 min, the animals were treated with 1 mg/kg scopolamine. Scopolamine is an amnesiac agent that is known to diminish local glutamate levels.

Findings: After administration of scopolamine, hippocampal glutamate levels decreased to approximately 89% of the pre-injection baseline levels. Both drug candidates, CB8411 and CB2233, attenuated the decrease in glutamate levels to about 94% of pre-injection baseline levels.

Conclusion & Significance: CB8411 and CB2233 have previously been shown to increase memory in non-human primates. We demonstrate that this effect may be caused via modulation of glutamate in the hippocampus and subsequent enhancement of working memory. These candidates are suggested a new class of compounds that are likely to be useful in the symptomatic treatment of AD.

Biography

Michael Entzeroth is currently Chief Scientific Officer/Chief Operating Officer of Cennerv Pharma (S) Pvt. Ltd in Singapore, a company focused on the development of novel drugs for the treatment of central nervous diseases. From 2007 to 2013, he was the Deputy Director and Vice President Research and Development and Deputy Director of the Experimental Therapeutic Centre, Biopolis, Singapore. Previously, he was Chief Scientific Officer of S*²BIO Pte Ltd in Singapore and between 1999 and 2002, as Vice President of CEREP SA in France, he was a member of the Executive Management Committee. From 1985 to 1999, with Boehringer Ingelheim, Germany, he was responsible for a variety of drug discovery programs. A number of drug candidates, he worked on during his career, are either on the market or in advanced clinical stage. Over the years, results from his work have been published in more than 50 publications in peer-reviewed scientific journals.

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