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PROTECTIVE ACTION OF THE GHRELIN AGONIST, HM01, AGAINST BETA-AMYLOID-INDUCED TOXICITY: A FOCUS ON THE BRAIN-GUT AXIS IN MICE

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Introduction: Alzheimer's disease (AD) is the most common age-related cause of dementia, characterized by extracellular beta-Amyloid (Ab) plaques, and intracellular phosphorylated tau tangles in the brain. Ab deposits have also been observed in the gastrointestinal (GI) tract of AD patients and transgenic mice over expressing amyloid precursor protein (APP). Ghrelin, an orexigenic hormone exhibits gastrointestinal prokinetic effects and is reported to be neuroprotective against Ab-induced degeneration via growth hormone secretagogue receptor 1a (GHSR-1a).
Objectives: In our preliminary studies, HM01, an orally active GHSR-1a agonist, rescued intra-hippocampal Ab-induced memory deficits. Here we investigate if HM01 can protect against Ab induced functional enteric nervous system (ENS) deficits and also memory deficits resulting, from Ab seeded into the GI tract.
Methods: 2-month-old ICR male mice were anaesthetized with isoflurane (1-3%) in oxygen for a small mid-line laparotomy incision and the GI tract was exposed for micro-injections of oligomer Ab1-42 (5 sites, total dose: 20ug/mouse), or vehicle (saline, 2.5ul per site), into the muscular wall. After surgery mice were administered HM01 (10mg/kg, p.o., daily) or vehicle in drinking water. We determined the potential protective effect of HM01 using different memory tasks, 11 months post-surgery.
Results: The Ab seeds diffused via the serosa and submucosa to nearby areas, and internalized in cholinergic nerves. Some Ab injected into the corpus of the stomach and proximal colon was retained for at least 1 month, and was partly re-distributed to the fundus and jejunum, causing neuromuscular coupling deficits. 11 months post-surgery, there were significant memory impairments in the Ab group compared with the vehicle control, as revealed in Y-maze spontaneous alteration and novel object recognition tests ($P<0.001$); HM01 prevented the memory impairments induced by Ab seeds ($P<0.05$).
Conclusion: Orally HM01 prevented cognitive impairments induced by Ab injected locally into the GI tract; it also prevented local neuromuscular coupling deficits. Taken together with data from our intra-hippocampal Ab-induced memory deficit studies, HM01 may have benefit in the early treatment of AD.

Disclosure of Interest: None Declared

Keywords: Beta-Amyloid, Brain-Gut Axis, Ghrelin Agonist HM01