COGNITIVE AND METABOLIC EFFECTS OF ORAL GALACTOSE IN STREPTOZOTOCIN-INDUCED RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE

PhD Thesis Proposal: Therapeutic potential of oral galactose on cognitive and metabolic changes in experimental models of Alzheimer's disease

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INTRODUCTION:

Sporadic Alzheimer's disease (sAD) is associated with dysfunction of the brain insulin receptor signaling and decreased glucose metabolism and energy in the brain which have become new targets in sAD therapeutic strategy. D-galactose, a C-4-epimer of D-glucose, could be considered as an alternative source of energy but can also stimulate secretion of glucagon-like peptide 1 (GLP-1), an incretin which stimulates insulin release and has its own neuroprotective activity. Our preliminary research in a streptozotocin-induced (STZ-icv) rat model of sAD demonstrated that one month of oral galactose treatment initiated immediately after STZ-icv administration successfully prevented the development of STZ-icv induced cognitive deficits. With this research we aimed to explore if oral galactose treatment could improve already developed cognitive deficit in the STZ-icv rat model and which mechanisms might be involved.

MATERIALS AND METHODS:

Two-month oral galactose treatment (200 mg/kg/day) was initiated 1 month (Exp 1/early sAD stage) and 4 months (Exp 2/medium sAD stage) after STZ/buffer-icv injection (3 mg/kg) in 3-months old male Wistar rats. Cognitive performance was tested by Morris Water Maze (MWM) and Passive Avoidance (PA) test. The level of GLP-1 (active/total), insulin, glucose and galactose was measured by ELISA immunoassay in plasma and cerebrospinal fluid (CSF). Brain glucose metabolism was measured *in vivo* by [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning. Data was analyzed by Kruskal-Wallis, followed by Mann-Whitney U test and 2-way ANOVA for repeated measures ($p<0.05$).

RESULTS:

STZ-treated animals showed cognitive decline in both experiments compared to their respective control (-85% PA, +93% MWM/Exp1; -78% PA, +71% MWM/Exp 2; $p<0.05$), while galactose treatment successfully improved cognitive deficit only in Exp 1 (+349% PA, -36% MWM; $p<0.05$). FDG-PET scan indicated a time-dependent mild decrement in glucose metabolism in the brain of STZ-treated rats compared to the controls in both experiments (-3% Exp 1; -12% Exp 2) which was increased (+14% Exp 1; +38% Exp 2) by oral galactose treatment in STZ-icv rats. The level of active GLP-1 was found decreased in plasma of STZ-treated rats compared to the controls only in Exp 1 (-51%, $p<0.05$) which was normalized by galactose treatment (+70%, $p<0.05$). Compared to the untreated controls, galactose-treated control rats demonstrated decreased levels of active GLP-1 in plasma (-80%, $p<0.05$) and total GLP-1 in CSF (-31%, $p<0.05$) in Exp 1 only. Plasma and CSF insulin levels were remained unchanged regardless the treatment in both experiments.

DISCUSSION:

Our preliminary results indicate that 2-month oral galactose treatment has a potential to normalize previously developed cognitive deficits in a STZ-icv rat model in early but not in medium-stage of experimental sAD. The mechanism of this cognitive improvement in early sAD stage might be the stimulation of GLP-1-mediated effects, as shown by increments in total/active GLP-1 plasma levels found previously decreased only in early stage of sAD in the STZ-icv rat model. Since oral galactose-induced improvement in brain glucose metabolism in the STZ-icv rat model was manifested both in early and medium stage of diseases, this mechanism does not seem to be the major contributor to the beneficial effects of oral galactose on cognitive impairment.

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MeSH / Keywords: Alzheimer's disease; streptozotocin; galactose; fluorodeoxyglucose F18; glucagon-like peptide 1; cognition; metabolism