

# THERAPEUTIC POTENTIAL OF ORAL GALACTOSE IN TRANSGENIC MICE MODEL OF ALZHEIMER'S DISEASE

Preliminary PhD title: Therapeutic potential of oral galactose in experimental Alzheimer's disease

PhD candidate: Ana Babić, mag. pharm.

Mentor: prof. dr. sc. Melita Šalković-Petrišić

Affiliation: Department of Pharmacology, University of Zagreb, School of Medicine, Šalata 11, Zagreb, Croatia

## INTRODUCTION

Sporadic Alzheimer's disease (sAD) is associated with dysfunction of the brain insulin receptor (IR) signaling followed by decreased glucose transport via glucose transporter GLUT4 and decreased glucose metabolism and energy in the brain<sup>1</sup>. D-galactose is the C-4-epimer of D-glucose and could be considered as an alternative source of energy (Fig. 1) but can also stimulate secretion of glucagon-like peptide 1 (GLP-1) which further stimulates insulin release and has also neuroprotective activity itself (Fig. 2).

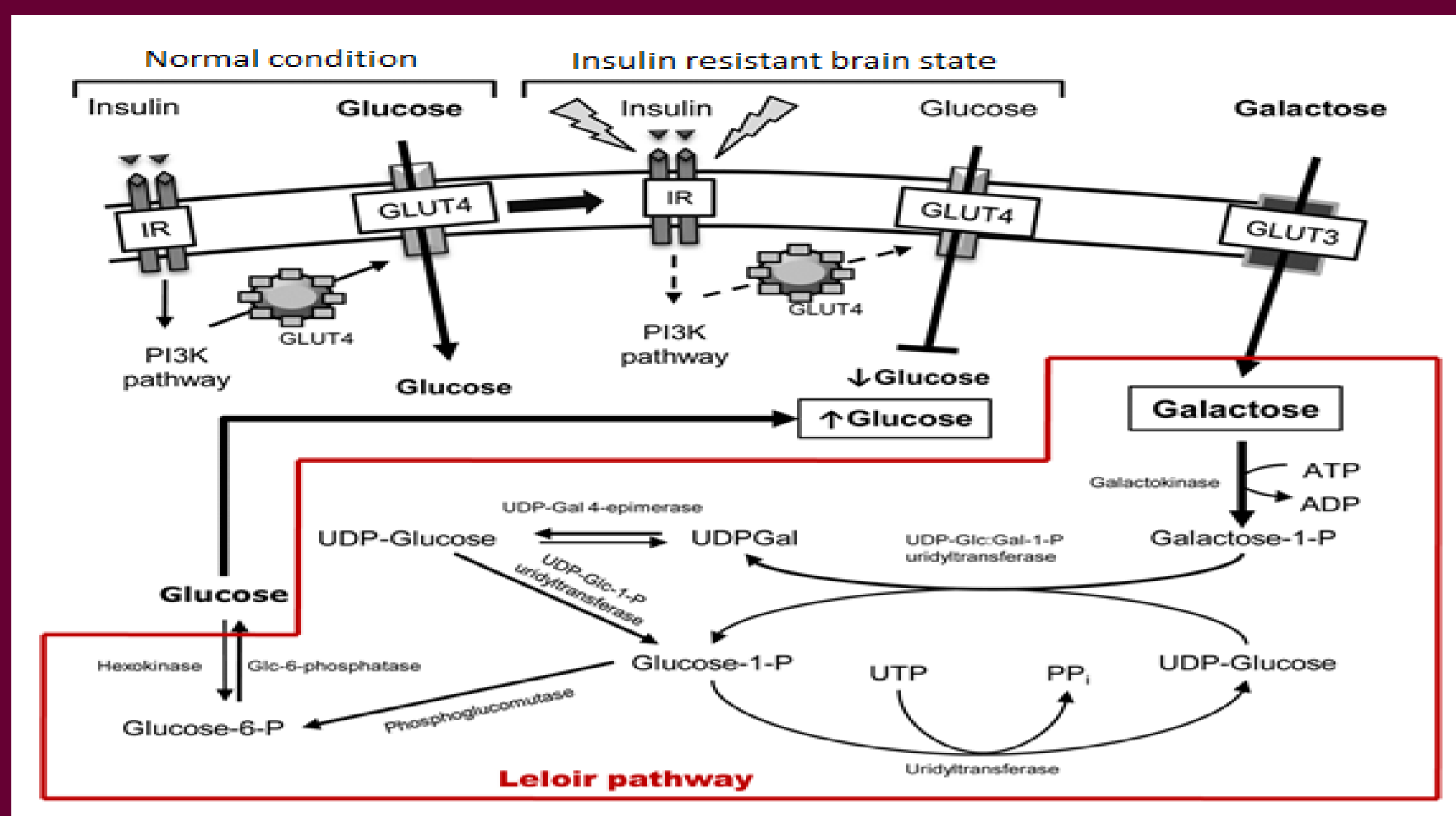


Figure 1. Intracellular conversion of galactose to glucose (modified after Šalković-Petrišić et al., 2014)<sup>2</sup>

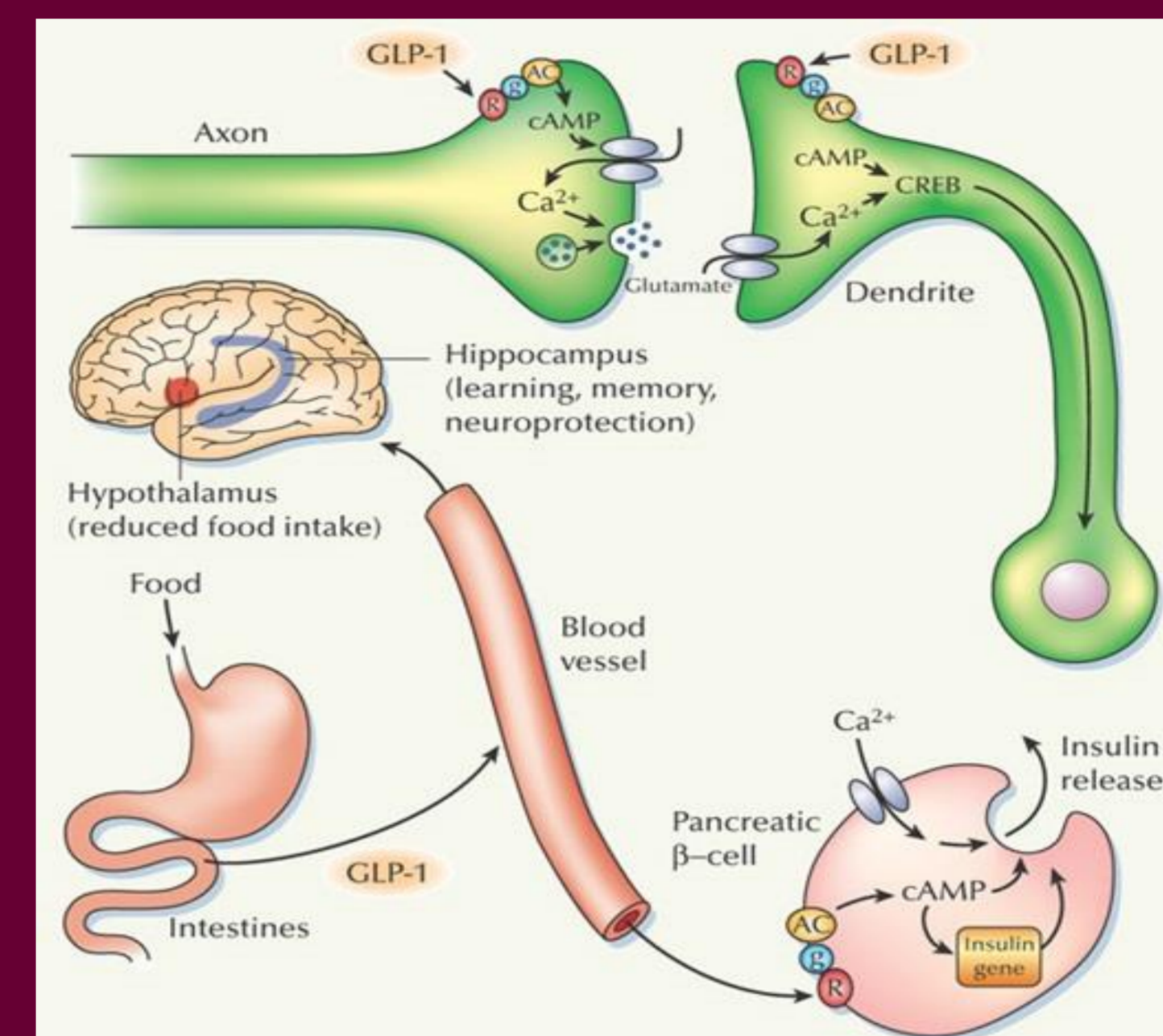


Figure 2. GLP-1 receptors located on neurons in the hippocampus, which is involved in learning, memory and neuroprotection<sup>3</sup>

Preliminary research of our group in a non-transgenic streptozotocin-induced (STZ-icv) rat model of sAD demonstrated that one month of oral galactose treatment initiated immediately after the STZ-icv administration, successfully prevented development of the STZ-icv induced cognitive deficits independently of the rat age and the galactose dose (100 to 300 mg/kg/day)<sup>2</sup>.

## HYPOTHESIS

Depending on the time of the treatment initiation, chronic oral galactose treatment may prevent the appearance of cognitive deficits or mitigate already developed cognitive deficits and/or plaque formation in transgenic Tg2576 mice which overexpress a mutant form of amyloid precursor protein (APP), and represent a model of familial AD.

## AIMS

- 1) To elucidate the possible therapeutic potential of oral galactose on cognitive deficits in transgenic mice model of familial AD
- 2) To evaluate possible underlying mechanisms of therapeutic effects of oral galactose in neurodegeneration at the level of brain glucose metabolism and IR signalling as well as amyloid  $\beta$  ( $A\beta$ ) and tau protein pathology

## MATERIALS, METHODS AND RESEARCH PLAN

**Animals:** male transgenic B6;SJL-Tg(APP<sup>SWE</sup>)2576Kha mice (Tg2576 mice, Taconic, Hudson, NY, USA) and wild type (controls).

**Experimental design:** Since Tg2576 model develops cognitive deficits at the age of 6 months and plaques at the age of 11 month, galactose treatment (200 mg/kg/day p.o. for 2 months) will be initiated before the appearance of cognitive deficits in the **neuropreventive design** (5 month-old mice) and before the appearance of plaques in the **neurorescue design** (10 month-old mice).

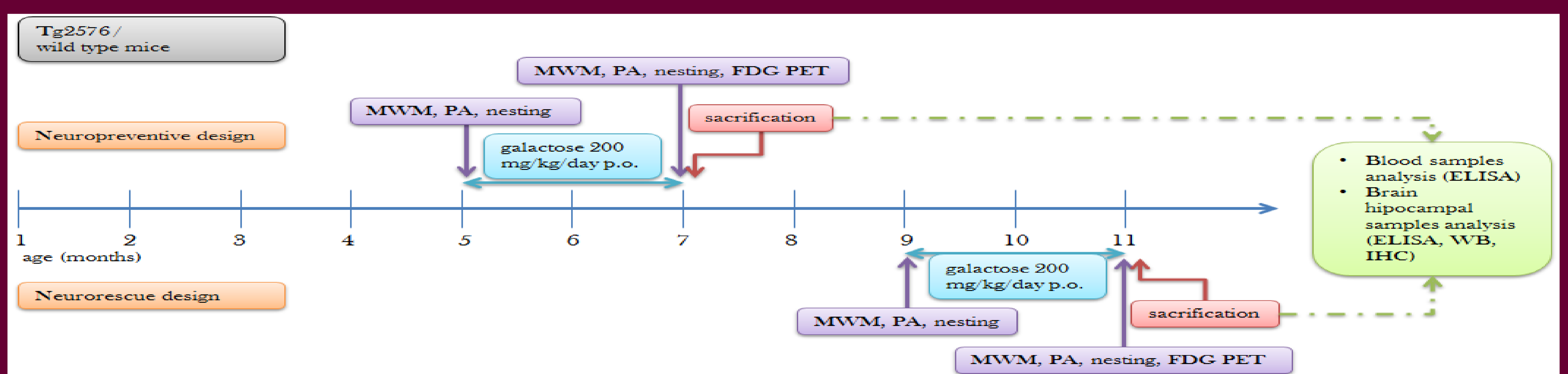
**Cognitive testing:** Morris Water Maze (MWM), Passive Avoidance (PA) and nesting test, before and after the galactose treatment.

**Fluorodeoxyglucose (FDG) PET scanning:** in vivo measurement of glucose metabolism in the brain after the galactose treatment.

**Neurochemistry:** SDS-PAGE electrophoresis and Western blot analysis (WB) for GLP-1 receptor (GLP-1R), GLUT3/4, insulin degrading enzyme (IDE), glycogen synthase kinase 3  $\beta$  (GSK3- $\beta$ ), and phospho (PHF1)/total tau in hippocampal tissue samples.

**Biochemistry:** ELISA immunoassay for GLP-1 (active/inactive), insulin, glucose and galactose in blood, and  $A\beta$ 1-42 in hippocampus.

**Histology:** immunohistochemistry (IHC/whole brain) for synaptophysin/synapses, AT8 phospho-tau, GFAP/astrocytes and NeuN/neurons.



## EXPECTED SCIENTIFIC CONTRIBUTION

Characterization of the therapeutic potential of oral galactose treatment on memory deficits and AD-like neurochemical and structural changes in the brain of widely used transgenic mice AD model as a new potential therapeutic strategy in AD treatment.

## LITERATURE

1. Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol. 2004;490:115-125.
2. Salkovic-Petrisic et al. Long-term oral galactose treatment prevents cognitive deficits in male Wistar rats treated intracerebroventricularly with streptozotocin. Neuropharmacology. 2014;77:68-80.
3. Mattson et al. Learning from the gut. Nat Med. 2003;9:1113-1115.

## ACKNOWLEDGMENT

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