

ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Candidate: Tereza Červinková

Supervisor: PharmDr. Lukáš Červený, Ph.D.

Title: Beneficial Effects of 11 β -HSD1 Inhibition on Cognitive Performance in a Mouse Model of Alzheimer's Disease

The increased life expectancy goes hand in hand with ageing-related cognitive impairments. Alzheimer's disease (AD) is the most common type of dementia being an irreversible and progressive brain disorder with loss of cognitive functions. Recent studies suggest that excess of glucocorticoid (GC) action exerts deleterious effects on the hippocampus and causes impaired spatial memory. In addition, it has been demonstrated that aged mice with cognitive deficits show increased gene expression of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) in the hippocampus and parietal cortex. The Senescence-Accelerated Mouse Prone 8 (SAMP8) strain is a spontaneous animal model of accelerated ageing. Many studies indicate that SAMP8 harbour the behavioural and histopathological signatures of AD.

In the present study, we evaluated the neuroprotective effects of 11 β -HSD1 inhibition by a potent pyrrolidine-based compound RL-118 and/or effects of diet on cognitive performance in different groups of SAMP8 by conducting behavioural and cognitive tests. In mice treated with RL-118, we observed changes in anxiety, improved motivation and social behaviour, as well as ameliorated cognitive performance in both spatial and recognition memories.

Obtained results suggest that the used substance RL-118 is a potent 11 β -HSD1 inhibitor with future potential in AD treatment.