11B-HSD1 INHIBITION RESCUES COGNITIVE DISTURBANCES AFTER CHRONIC MILD STRESS IN MICE: TARGET ENGAGEMENT DETERMINATION THROUGH TAPS ASSAY

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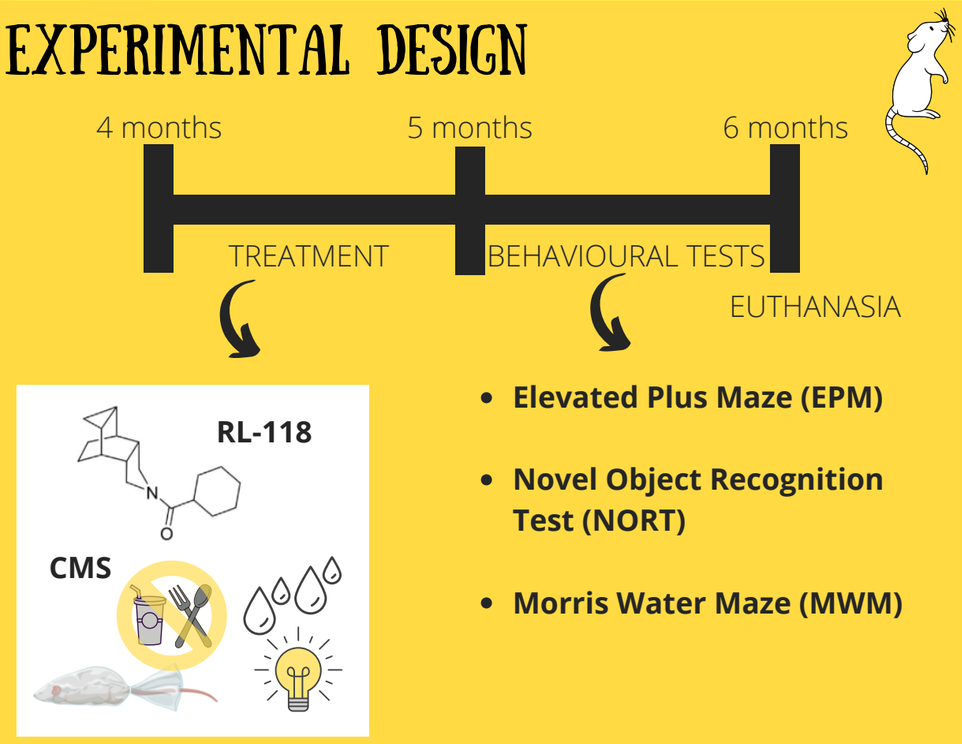
INTRODUCTION

With the increase in life expectancy, the study of **age-related diseases** and the development of different strategies to deal with them become mandatory. Cognitive and behavioural disturbances are growing public healthcare issue for the modern society, which is experiencing an increasingly common **stressful lifestyle**. Taking into consideration the convergence of aging, stress and neurodegenerative diseases, such as AD, there is impaired **glucocorticoid (GC) signalling**. Therefore, the study of GC-mediated stress response to chronic moderate stressful (CMS) situations, as account in the daily life, becomes of huge interest in order to design pharmacological strategies to prevent neurodegeneration. Several pieces of evidence link the **inhibition of 11β-HSD1** with reduction of GC levels and **cognitive improvement**, while CMS exposure has been associated with reduced cognitive performance.

The aim of this project was to assess whether RL-118 treatment, an 11β-HSD1 inhibitor, could restore the deleterious effects of CMS on cognition and behavioural abilities, but also acts on molecular mechanisms that compromise healthy aging in SAMP8 mice.

EXPERIMENTAL DESIGN



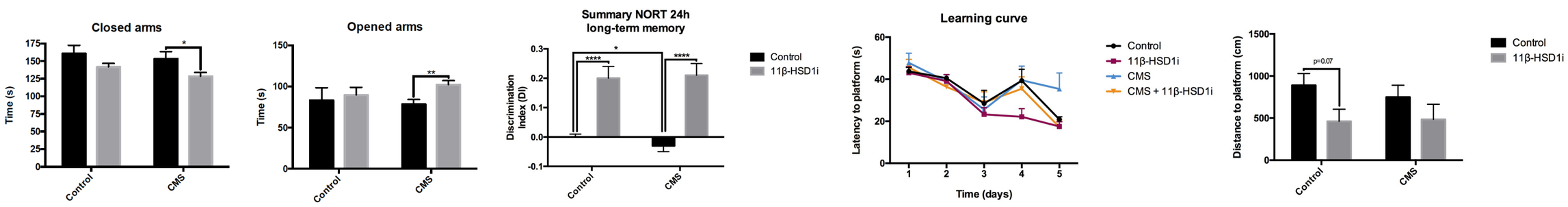
- **Elevated Plus Maze (EPM)**
- **Novel Object Recognition Test (NORT)**
- **Morris Water Maze (MWM)**

CONCLUSIONS

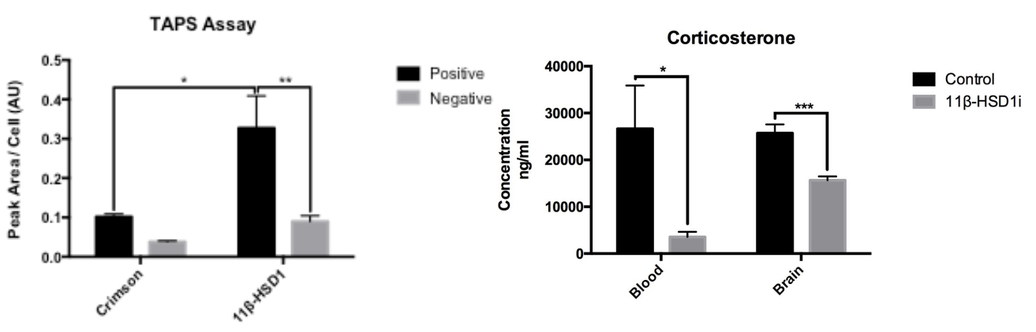
- Specific target engagement between RL-118 drug and its target, the 11β-HSD1 enzyme was determined. Therefore, all the effects observed in SAMP8 mice treated with the drug described can be attributed to the inhibition of this enzyme.
- RL-118 drug is capable of crossing the BBB into the brain of SAMP8 mice, as the effects that result from 11β-HSD1 enzyme inhibition are observed in both blood and cerebral tissues.
- CMS declined cognitive and behavioural abilities, as well as neurogenesis and antioxidant mechanisms, while modulated epigenetic markers and increased inflammatory signalling and Aβ formation and accumulation.
- 11β-HSD1 inhibition through RL-118 turned up to restore the majority of these detrimental effects caused by CMS

RESULTS

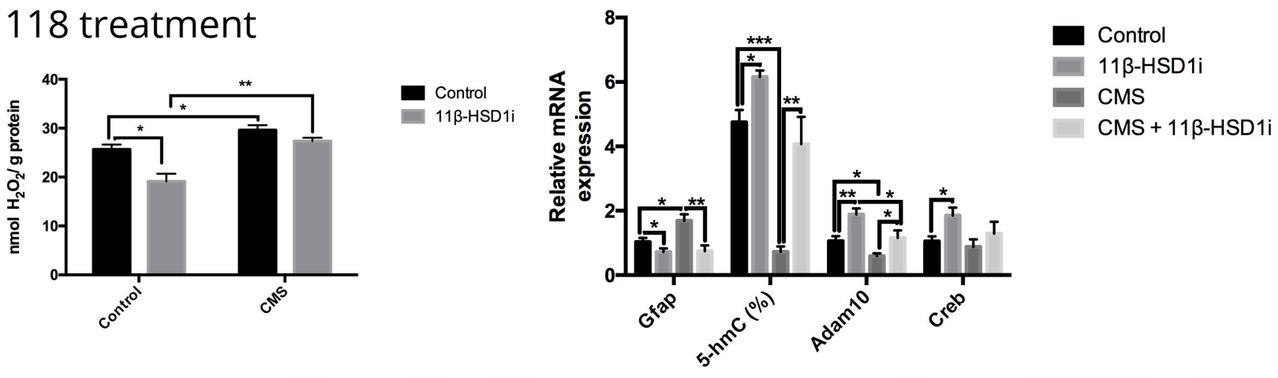
Cognitive improvement and risk-taking behaviour reduction after 11β-HSD1 inhibition and recovery in mice under CMS exposure

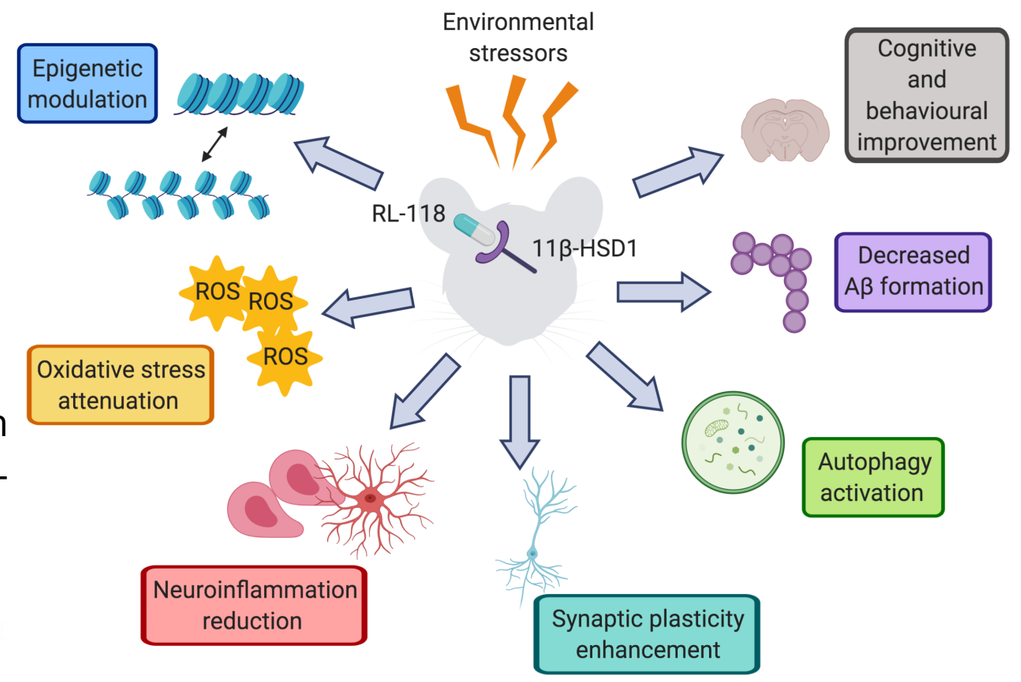


11β-HSD1 and RL-118 target engagement and corticosterone decrease after drug treatment



Oxidative stress attenuation, epigenetic changes, neuroinflammation and Aβ reduction as well as neurogenesis enhancement induced by RL-118 treatment





Values are the Mean ± Standard error of the mean (SEM) (n = 8 for each group). Two-Way ANOVA following Tukey test; *p<0.05; **p<0.01; ***p<0.001.