Determination of target engagement through TAPS assay: behaviour and molecular analysis after RL-118 treatment, a potent 11β-HSD1 inhibitor

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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 situations, as account in the daily life, becomes of huge interest in order to design pharmacological strategies to prevent neurodegeneration.

To address this issue, we determined the target engagement between RL-118 and 11β-HSD1 and afterwards SAMP8 were exposed for 4 weeks to CMS paradigm and treated with RL-118, an 11β-HSD1 inhibitor. In fact, several pieces of evidence link the inhibition of this enzyme with reduction of GC levels and cognitive improvement and CMS exposure has been associated with reduced cognitive performance. The aim of this project was to assess whether RL-118 treatment could restore the deleterious effects of CMS on cognition and behavioural abilities, but also on molecular mechanisms that compromise healthy aging in SAMP8 mice.

On one hand, we determined the target engagement between RL-118 and 11β-HSD1 through TAPS assay, therefore all the beneficial effects described in SAMP8 treated with the drug can surely be attributed to the inhibition of this enzyme. Besides, herein we observed changes in epigenetic markers reversed after RL-118 treatment. In addition, CMS exposure, produced ROS damage accumulation, and increments of pro-oxidant enzymes as well as pro-inflammatory mediators through NF-κB pathway and astrogliosis markers, like *Gfap*. Of note, those modifications were recovered by 11β-HSD1 inhibition. Remarkably, although CMS altered mTORC1 signalling, autophagy was increased in SAMP8 treated with RL-118 mice. Also, we found amyloidogenic APP processing pathway favoured and decreased synaptic plasticity and neuronal remodelling markers in mice under CMS, but on the contrary, changed after RL-118 treatment. In consequence, detrimental effects on behaviour and cognitive performance were detected in CMS exposed mice, but restored after concomitant 11β-HSD1 inhibition by RL-118.

Overall, CMS is a feasible intervention to understand the influence of stress on epigenetic mechanisms underlying cognition and accelerating senescence. However and most important, 11β-HSD1 inhibition through RL-118 turned up to restore the majority of these detrimental effects caused by CMS, indicating that GC excess attenuation may become a potential therapeutic strategy for age-related cognitive decline and AD.