INTRANASAL ADMINISTRATION OF IRBESARTAN AS A NEW STRATEGY FOR ADDRESSING NEURODEGENERATION IN A NEUROINFLAMMATION MICE MODEL: PHARMACOKINETIC AND EFFICACY EVALUATION

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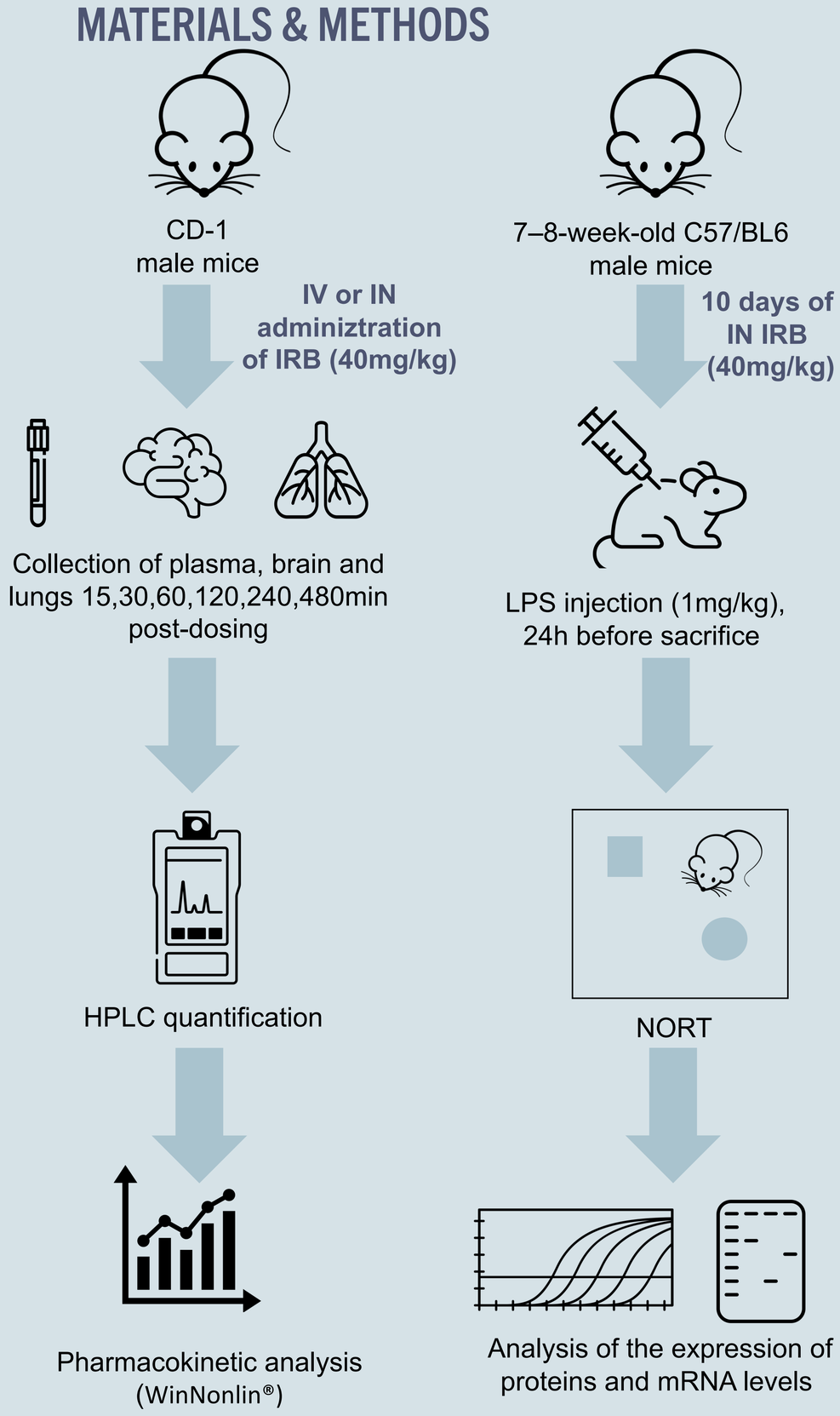
INTRODUCTION

- Approximately 50 million people worldwide are diagnosed with **Alzheimer's disease (AD)**.
- **Neuroinflammation** is a key player of neurodegenerative diseases, namely AD.
- The major cell survival **PI3K-Akt** pathway has been demonstrated to exert anti-neuroinflammation and anti-oxidative stress in neurons.
- **Renin-Angiotensin System (RAS)** acting drugs are evidencing a high potential to delay AD development, in hypertensive patients.
- However, **access to the brain** is strongly hampered by the blood-brain barrier (BBB).

OBJECTIVES

- Evalutate the pharmacokinetic profile of irbesartan (IRB) after **intranasal (IN)** or intravenous (IV) administration;
- Evaluate the direct passage of IRB to **the brain**;
- Evaluate the **efficacy** of IRB in a LPS-mice model of **neuroinflammaton.**

MATERIALS & METHODS



CONCLUSIONS

- **Intranasal administration** increases brain concentrations of irbesartan.
- **PI3K/AKT** plays an important role in the mechanism of action of Irbesartan.
- Irbesartan was able to **revert** the cognitive decline induced by LPS.

REFERENCES

1. Gouveia F, Camins A, Ettcheto M, et al.. *Ageing Res Rev*. 2022;77. doi:10.1016/j.arr.2022.101612
2. Nava Catorce M, Gevorkian G. *Curr Neuropharmacol*. 2016;14:155-164.

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RESULTS

PHARMACOKINETIC STUDIES

Figure 1

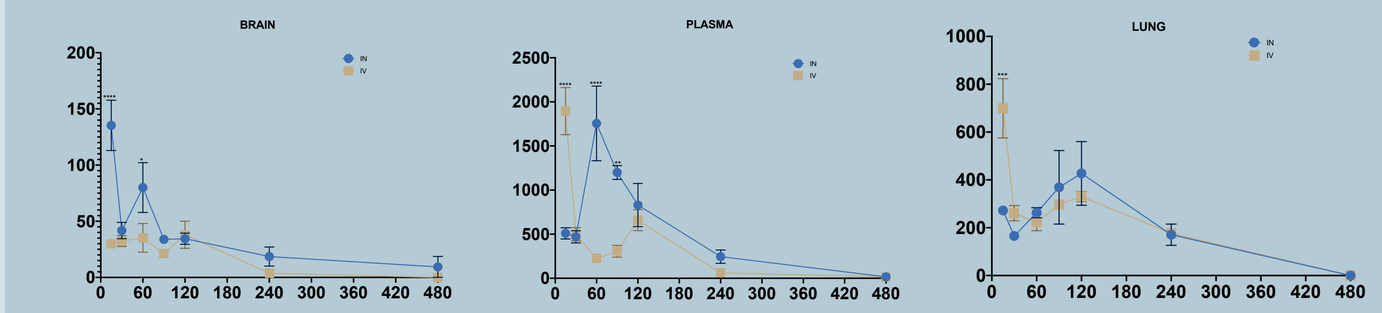

Figure 1. Graphical representation of A) brain, B) plasma and C) lung concentrations (ng/mL) of irbesartan up until 8h post-dosing. Values are the mean ± SEM (n=4 per time-point). Statistics: Two-way ANOVA followed by Sidak's multiple comparison test: *p < 0.05, ** p < 0.01 , *** p < 0.001 and **** p < 0.0001.

EFFICACY STUDIES

Figure 2

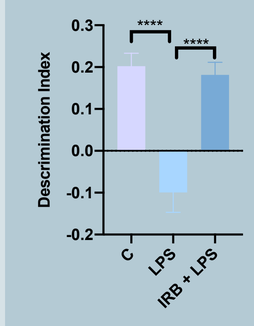

Figure 2. Descrimination index of the animals in the NORT. Values were calculated by using the following formula $(T_{nove}-T_{familial})/(T_{nove}+T_{familial})$, n= 24/experimental group. Statistics: Ordinary one-way ANOVA followed by Fisher's LSD test. p 0.05 was considered significant: **** p < 0.0001.

Figure 3

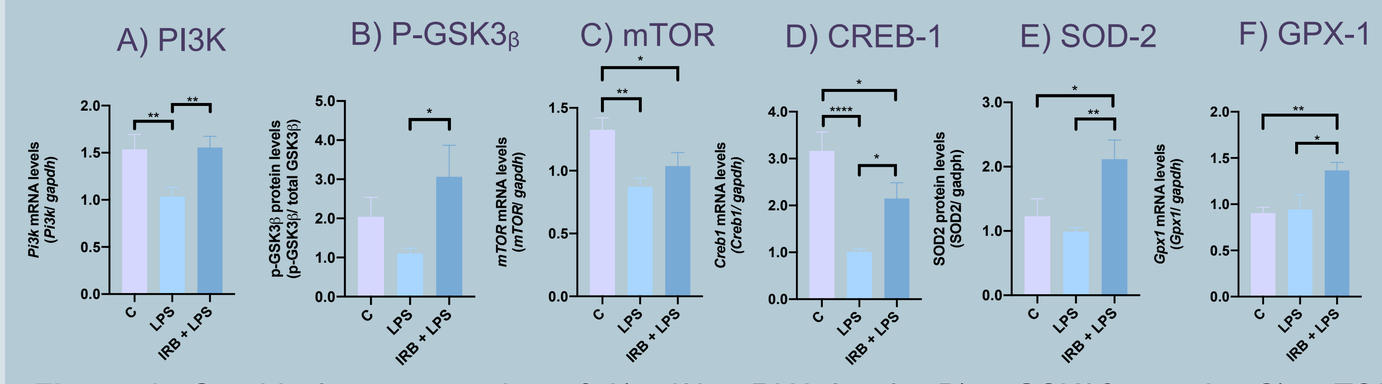

Figure 3. Graphical representation of A) *pi3k* mRNA levels, B) p-GSK3β protein, C) *mTOR* mRNA levels, D) *Creb1* mRNA, E) SOD2 protein levels, F) *Gpx1* mRNA levels after treatment with irbesartan, Values are the mean ± SEM of eight independent experiments expressed relatively to LPS non-treated mice. Statistics: Ordinary one-way ANOVA followed by Fisher's LSD test. p 0.05 was considered significant: *p < 0.05, ** p < 0.01 , **** p < 0.0001.

Figure 4

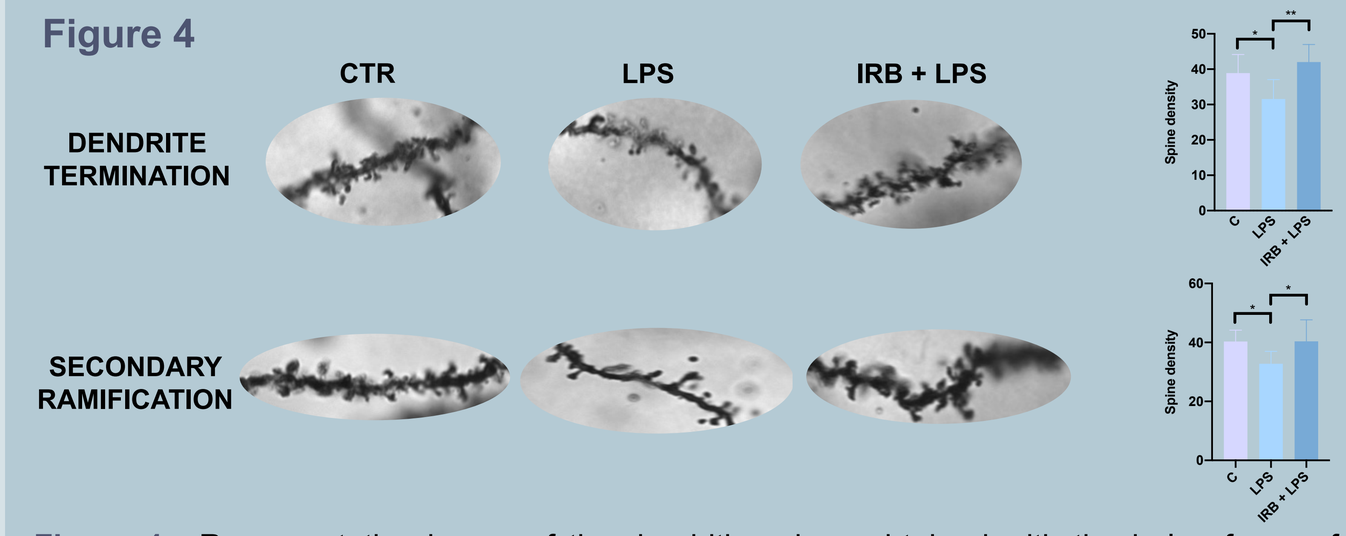

Figure 4. Representative image of the dendritic spines obtained with the help of a confocal microscope for each experimental group (Golgi stain). Differences on the number of dendritic spines in 30 µm sections of the pyramidal neurons of the prefrontal cortex (n = 6/experimental group) were found between the treatment group and the LPS group.

Figure 5

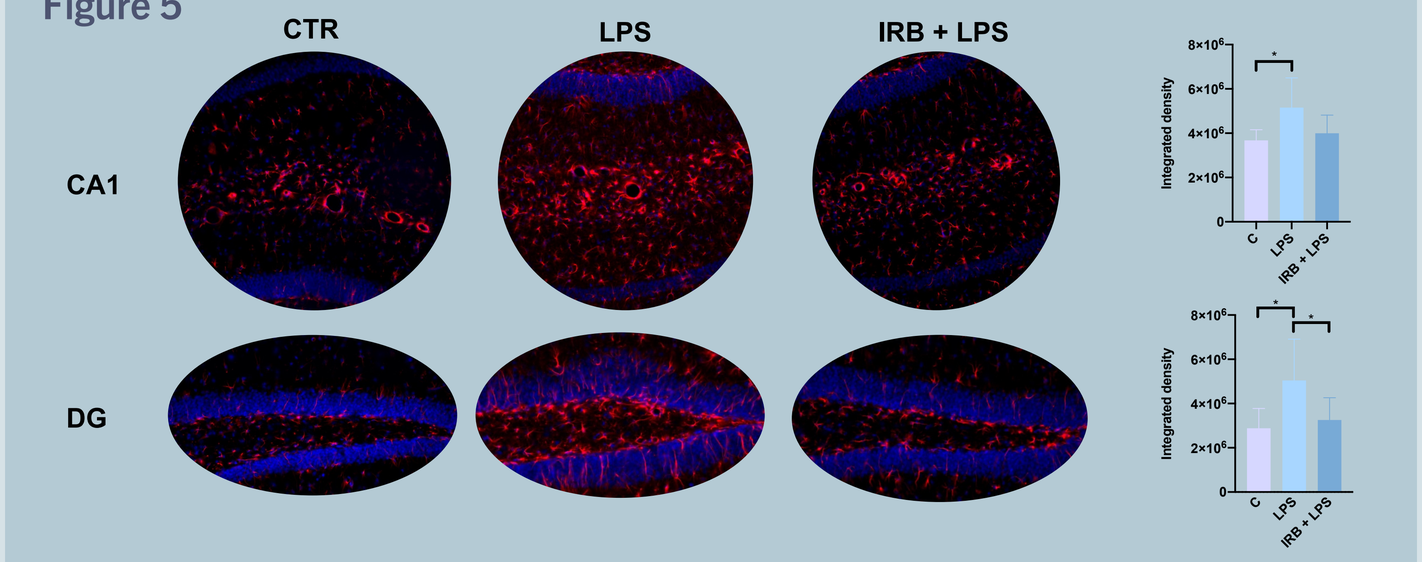

Figure 5. Representative images of GFAP-labeling (red) in the dentate gyrus and CA1 region of the hippocampus. Hoechst was used to stain the nuclei (blue). Differences in fluorescence intensity for GFAP were observed between treatment group and LPS group.