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Evaluating the window of opportunity for intranasal insulin therapy in a rat model of cerebral ischemia

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INTRODUCTION & AIM

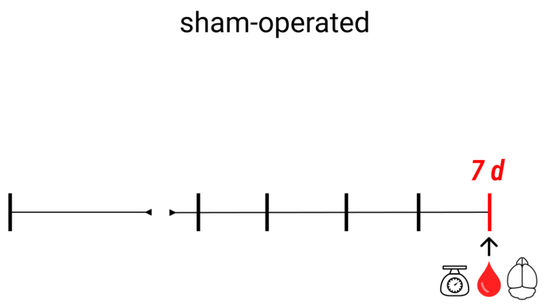
Cerebral ischemia is a significant medical and social issue, necessitating the development of effective treatment strategies. Due to the complex pathogenesis and prolonged recovery period associated with this condition, drugs with pleiotropic effects, such as intranasally administered insulin (INI), are of the greatest interest. INI sprayed in the nasal cavity enters the brain, regulating metabolism through central mechanisms, has neuroprotective and neuro-regulatory effects [PMID: 36834685]. It has been proven to be effective in the treatment of neurodegenerative diseases, although data on its effectiveness in cerebral ischemia remain limited. **For the first time, this study investigates the therapeutic window for INI in a rat model of transient global cerebral ischemia.**

METHOD

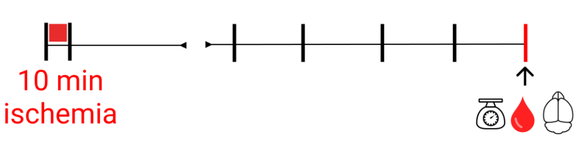
- 6-month old Wistar male rats, 400-450 g.
- Model of forebrain ischemia/reperfusion (IR): 10-min bilateral common carotid artery occlusion with hypotension (40 mm Hg) and subsequent reperfusion [doi: 10.1134/S0022093025030056]. Sham-operated (SO) controls underwent surgery without occlusion or hypotension.
- Treatment: intranasal injection of 0.5 IU/rat human recombinant insulin, Sigma, dissolved in citrate buffer, pH 4.4 or citrate buffer for SO- and IR-groups (not shown on scheme) after 2 h or 4 h post-IR, followed by once-daily dosing.
- On 7th postischemic day hippocampal gene expression were measured using RT-PCR and neuronal survival in CA1 region of hippocampus were assessed via Nissl staining.

Scheme of experiment

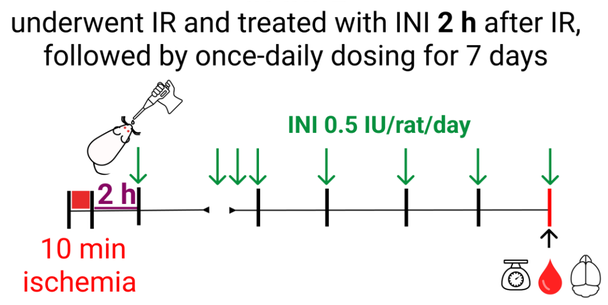
SO -
sham-operated



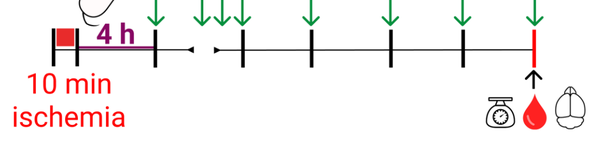
IR -
underwent brain ischemia/reperfusion



IR-INI-2
underwent IR and treated with INI **2 h** after IR, followed by once-daily dosing for 7 days



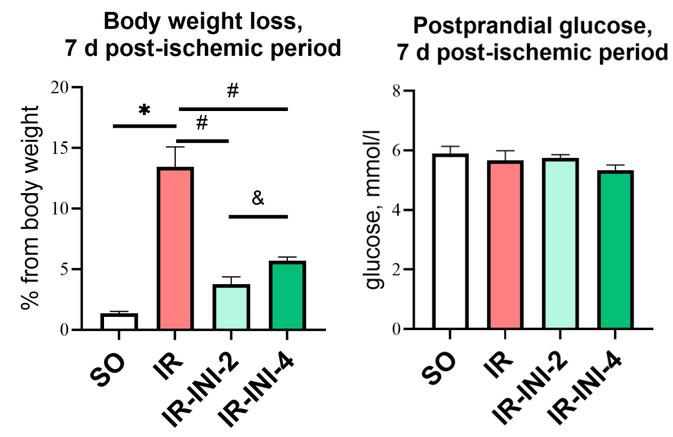
IR-INI-4
underwent IR and treated with INI **4 h** after IR, followed by once-daily dosing for 7 days



- Statistical analysis was performed using GraphPad Prism 8.0.1. The Shapiro-Wilk test was used to assess normality. For two-group comparisons, Student's t-test was applied. Multiple group comparisons were performed using one-way ANOVA with Bonferroni's post-hoc test for normally distributed data, or the Kruskal-Wallis test with Dunn's post-hoc test for non-normal data. Normally distributed data are presented as mean ± SEM; non-normal data as «box-and-whiskers» plots. A p-value < 0.05 was considered significant.

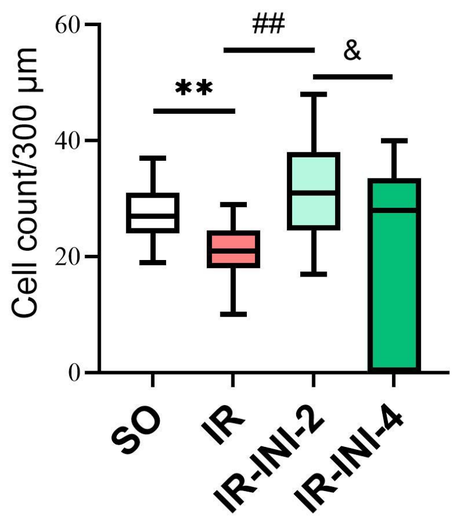
RESULTS & DISCUSSION

INI at 2 h post-ischemia more effectively prevented body weight loss in IR rats compared to the 4 h regimen without affecting glucose level

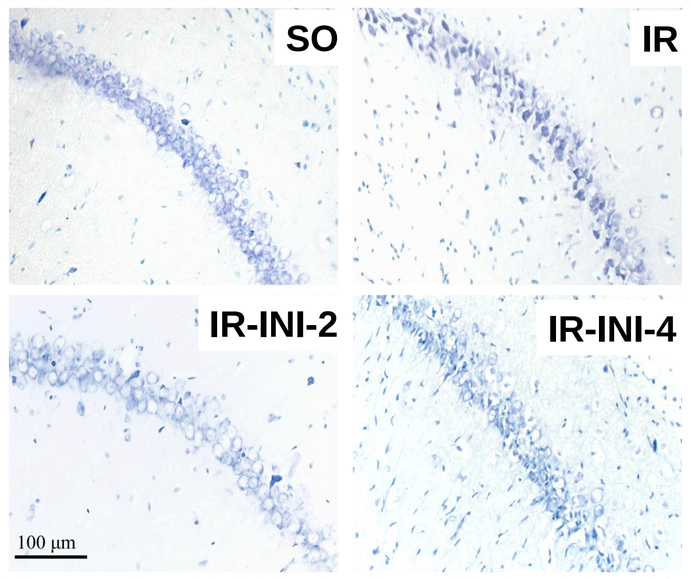


*, #, & – $p < 0.05$.

Neuroprotective effect of INI observed only in earlier treatment of IR-group

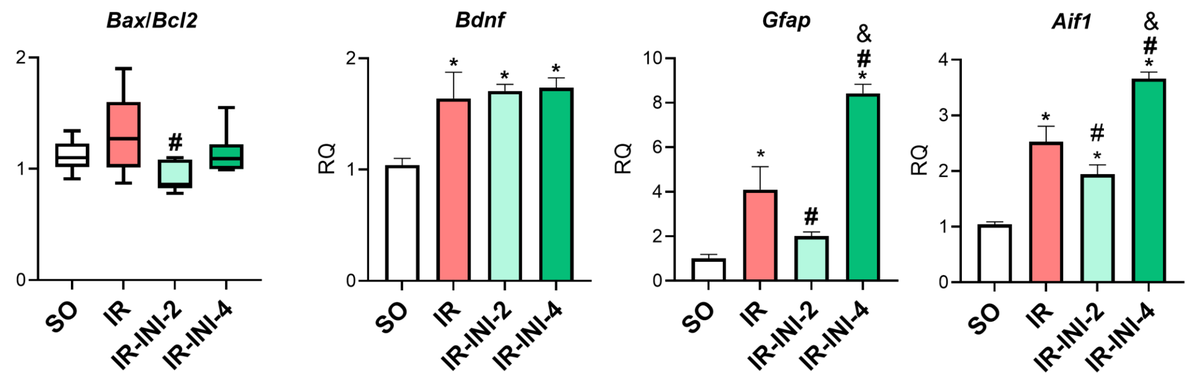


**, ## – $p < 0.01$; & – $p < 0.05$.



Micrographs of CA1 brain slices. Nissl staining, 20x.

Treatment with INI only at 2 h after IR decreases *Bax*/*Bcl2* ratio, *Gfap* and *Aif1* gene expression in rat hippocampus



* – compared to SO, # – compared to IR, & – compared to IR-INI-2, all $p < 0.05$.

CONCLUSION

This study is the first to define a critical window of opportunity for INI treatment in transient cerebral ischemia. Administration initiated within 2 h post-IR provides neuroprotection and attenuates glial activation, while delayed treatment (4 h) is markedly less effective.

FUTURE WORK / REFERENCES

We have obtained promising data indicating that INI exerts a neuroprotective effect in rats with type 2 diabetes mellitus (T2DM) subjected to IR. Furthermore, chronic INI was found to improve peripheral glucose sensitivity in T2DM rats [doi: 10.1134/S0022093024030190]. Future studies will investigate its therapeutic window in this comorbid pathology.

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