Cyclosporin A restricts rotavirus infection by enhancing type 1 interferon response in infected epithelial cells in vitro and in vivo

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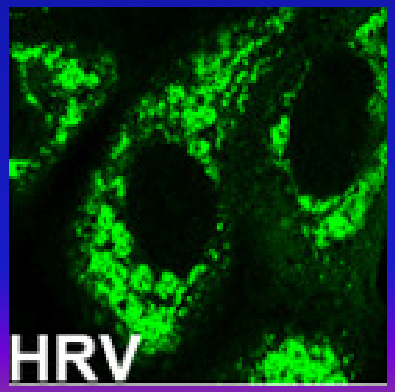
Chongqing, P.R.China

2014-9-26

Introduction

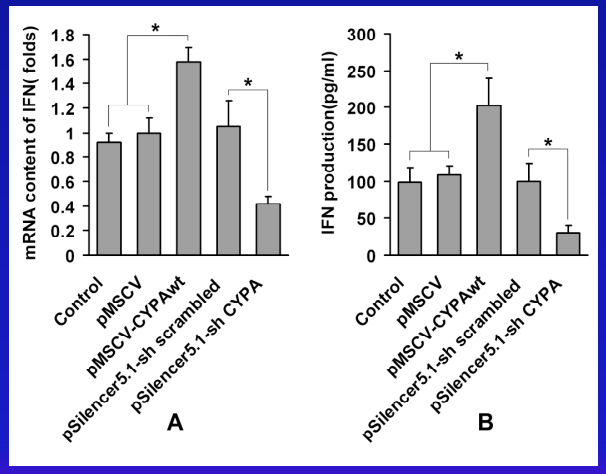
- Rotavirus infection is the major cause of deadly diarrhea of infants below 5 years old all over the world
- RV vaccines are neither globally distributed nor highly effective in some developing countries
- To date, no specific anti-rotavirus drug is available
- Cyclosporin A (CsA) has long been known to be a powerful immunosuppressive agent
- CsA can inhibit virus replication such HCV through a Cyclosphilin A dependent way



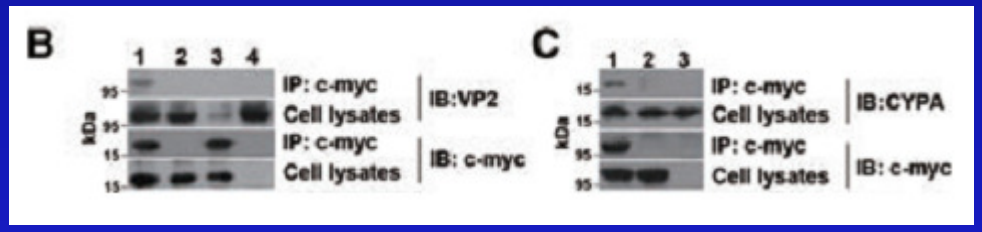




- Our previous studies showed that cyclophilin A (CYPA) play a critical role for rotavirus in subverting host cells IFN-β production
- CsA, the CYPA Prolyl isomerase inhibitor, can interact with CYPA through inhibiting CYPA PPIase activity
- Thus we hypothesized that CsA may be able to suppress rotavirus replication through IFN-β signaling pathway, and therefore reduce diarrhea

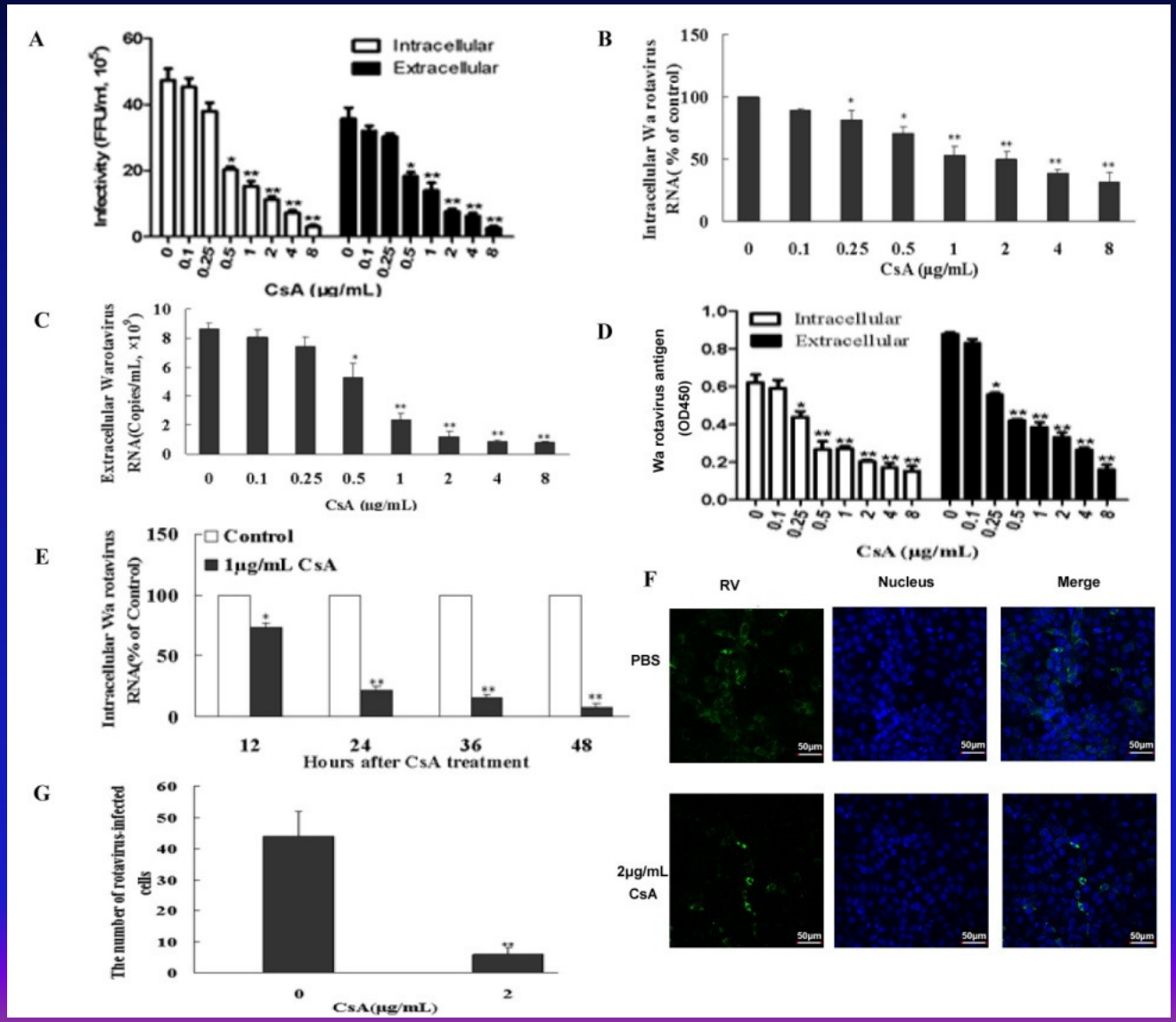


He, HY, et al. 2012, BBRC

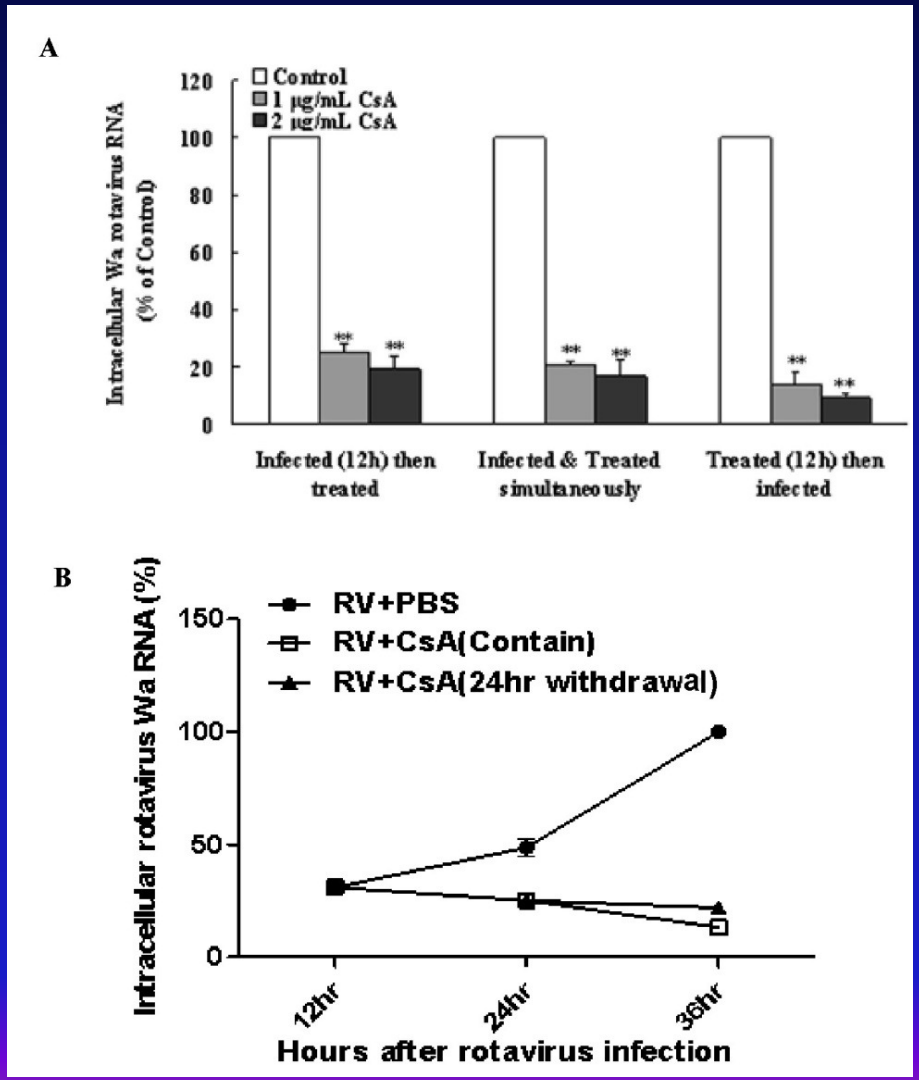


He, HY, et al. 2013 Proteomics,

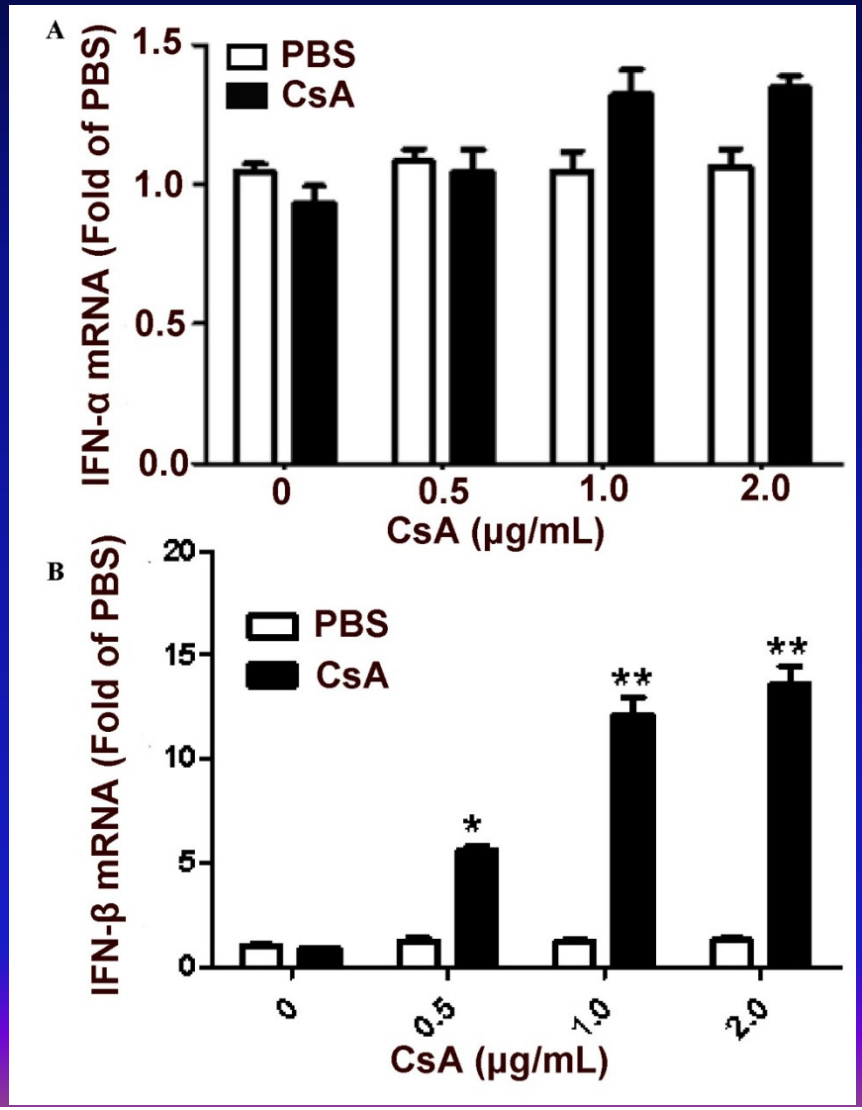
Cyclosporin A (CsA) can efficiently inhibit Wa rotavirus replication in vitro



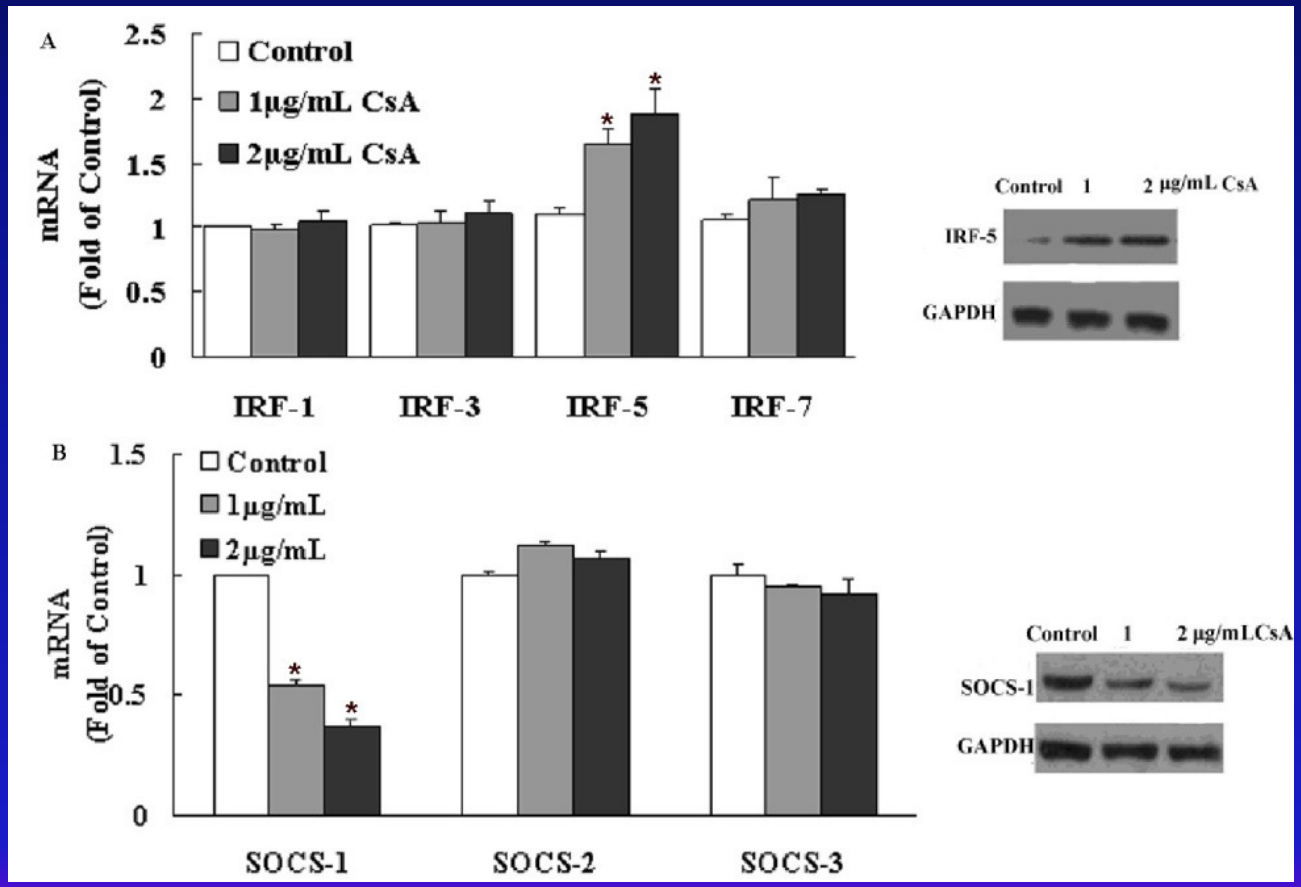
Cyclosporin A (CsA) can inhibit Wa rotavirus replication under various conditions



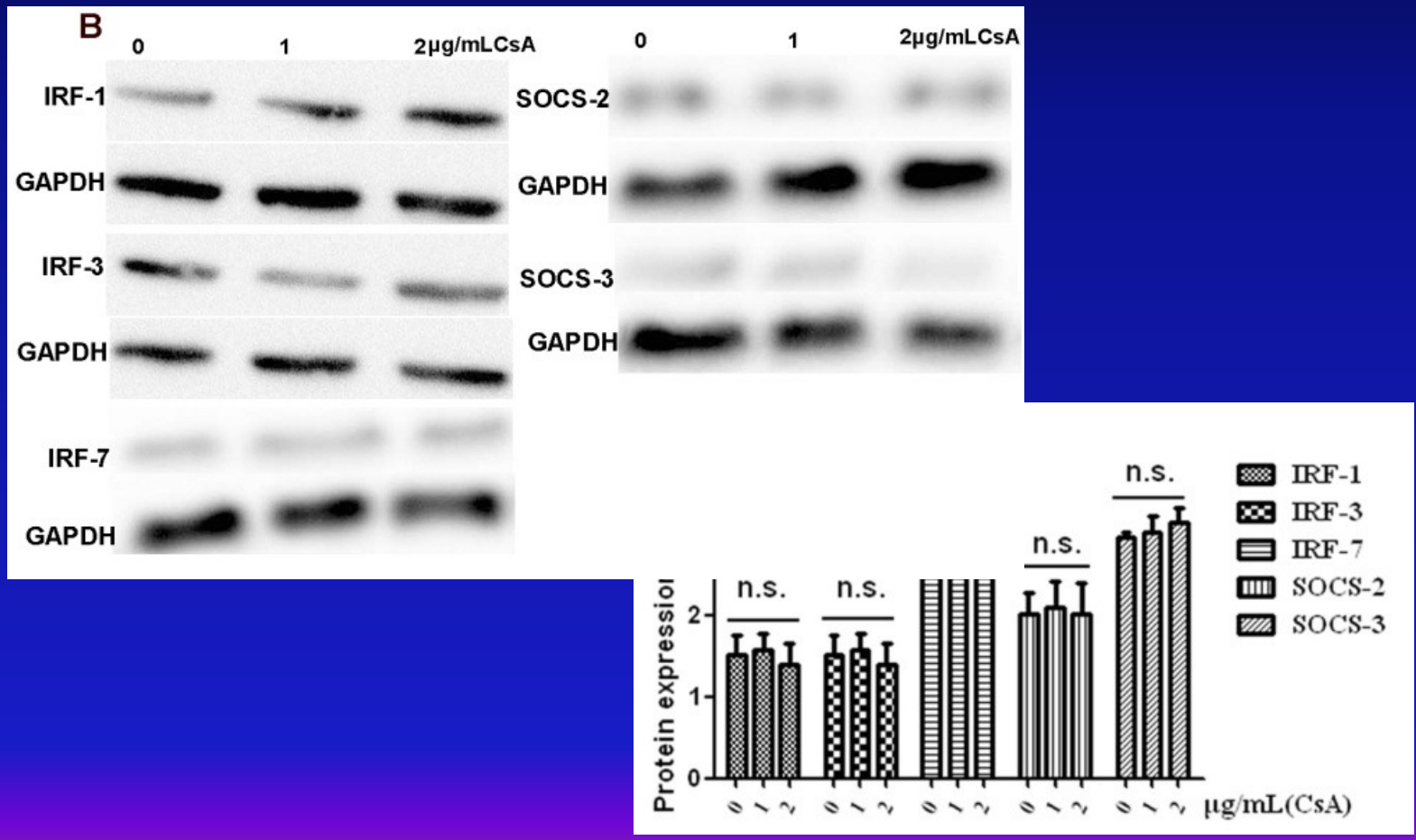
cyclosporin A (CsA) can promote IFN-β but not IFN-α expression



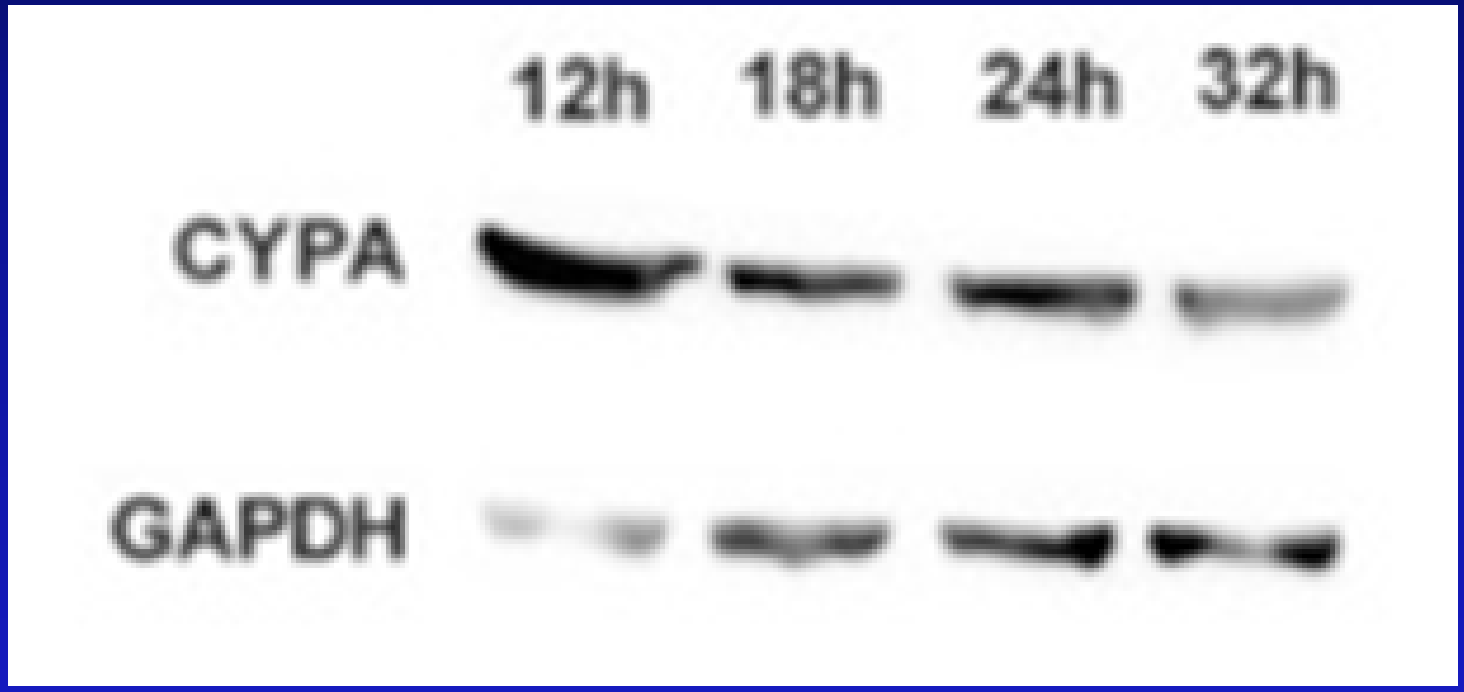
Effect of cyclosporin A (CsA) on the expression of the type I interferon (IFN) signaling pathway regulators



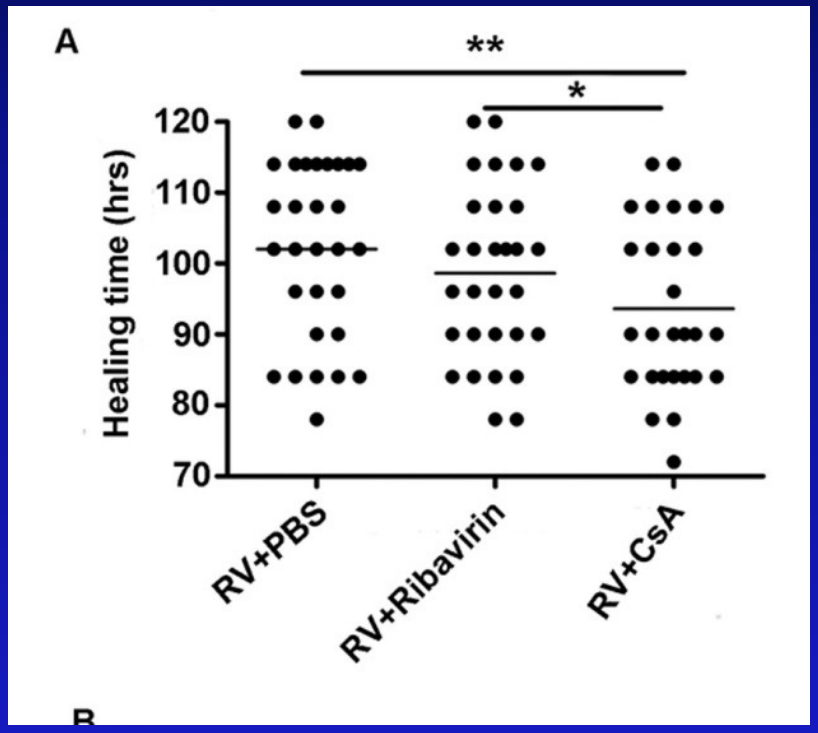
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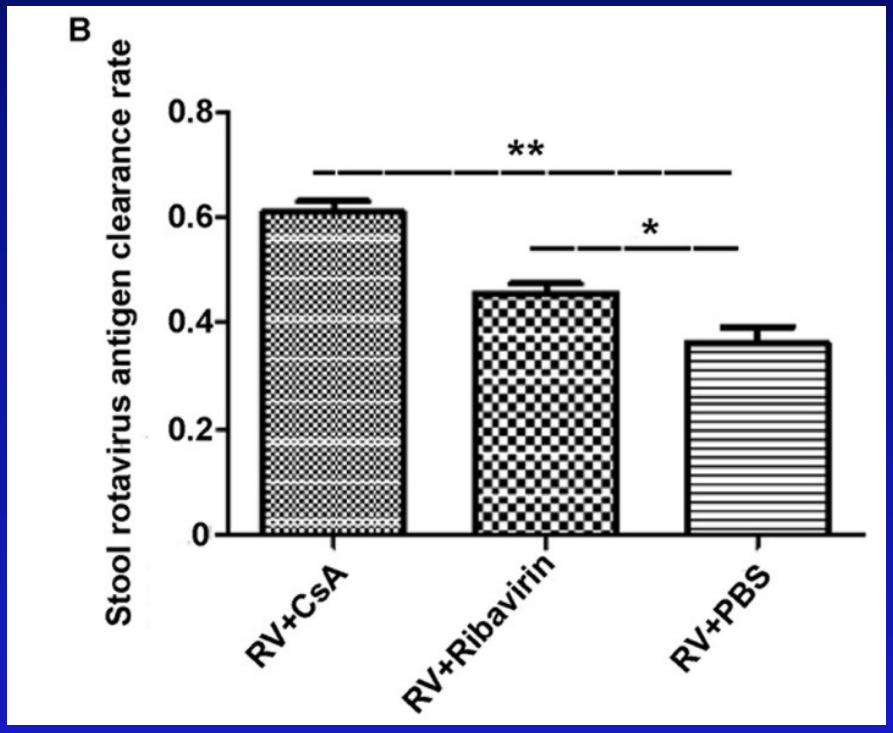


Expression patterns of CYPA in Wa rotavirus infected HT-29 cells with treated with CsA

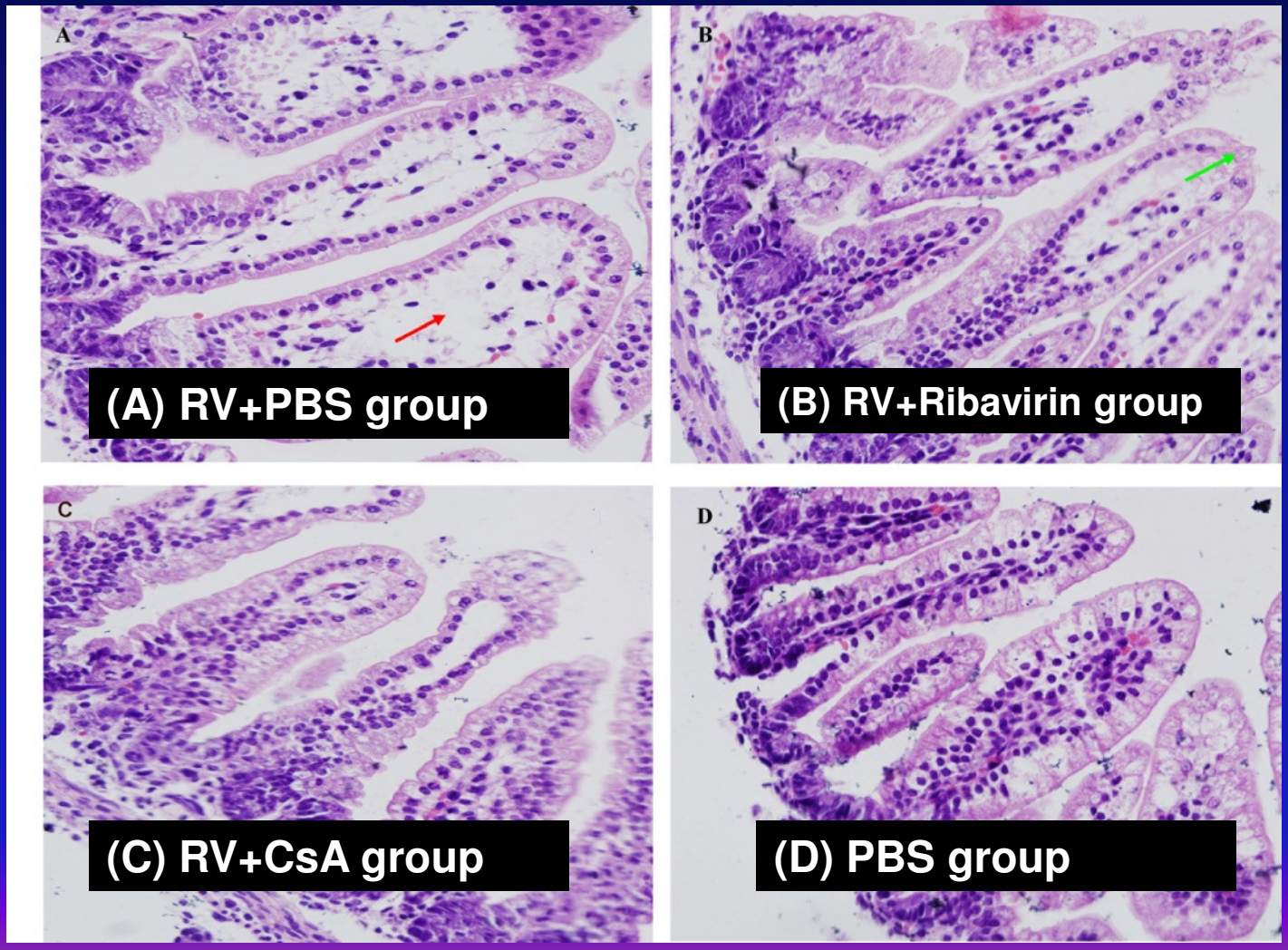


Effect of CsA on SA11 rotavirus-infected neonatal mouse model





Jejunum changes as assessed by histology using a light microscope

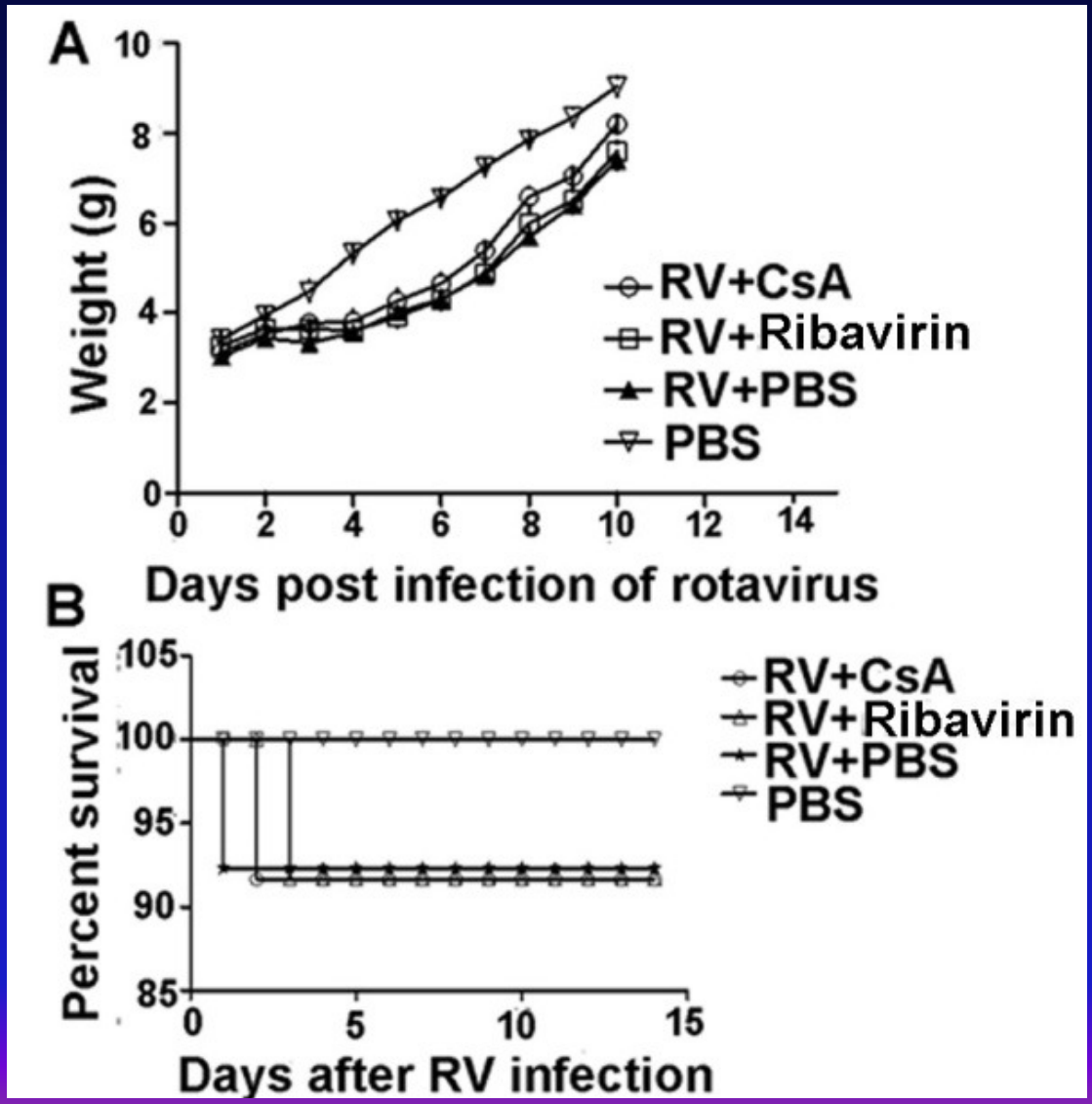


	RV+PBS group (control)	RV+Ribavirin group	RV+CsA group	PBS group
Villi height (µm)	296.15±43.64	280.92±49.17	301.13±55.25	313.54±18.25
Crypts depth (µm)	35.26± 2.48	26.54± 3.21*	26.01± 1.94*	30.19± 1.22

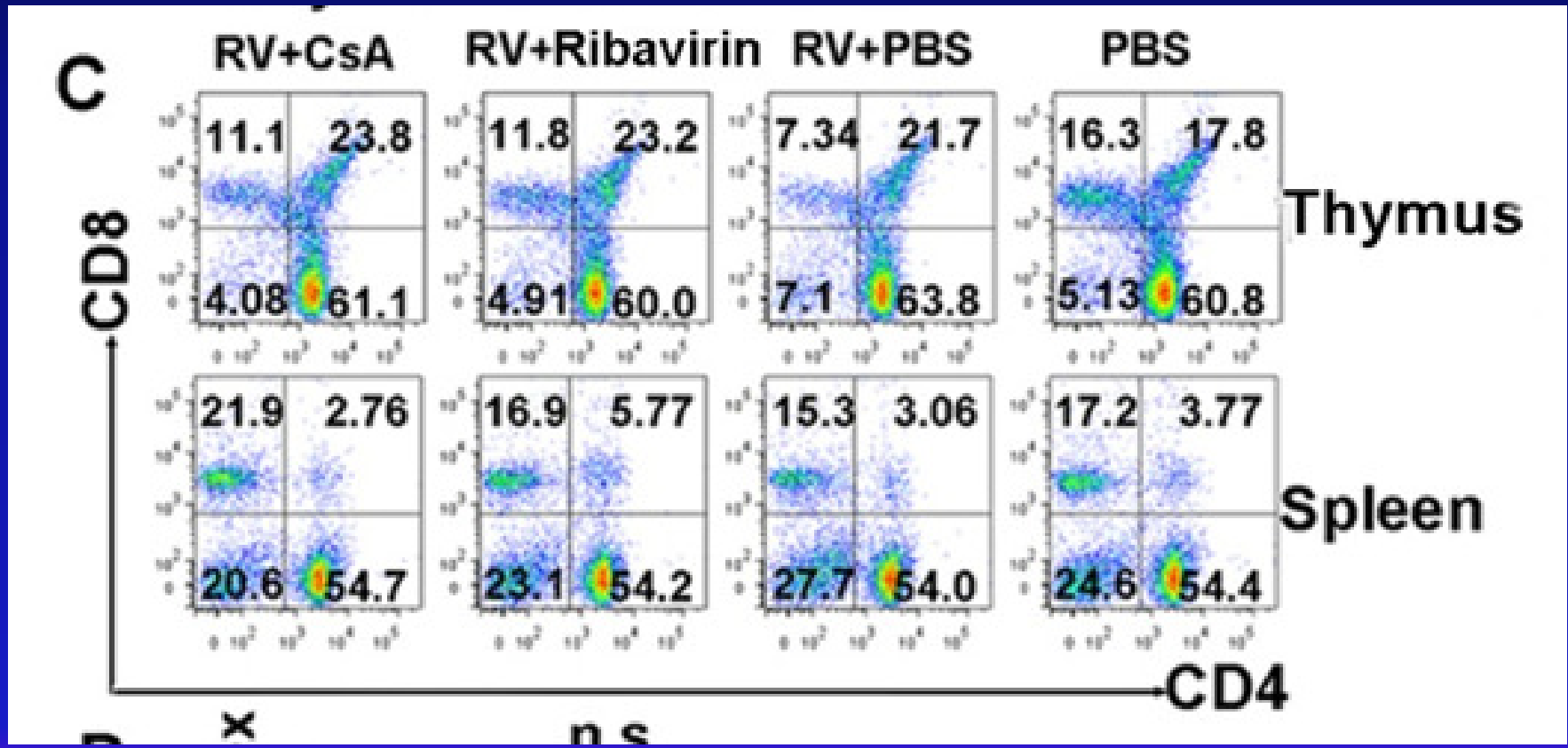
Data represents the mean±standard deviation (SD).

*Values are significantly different at $p<0.05$ from control.

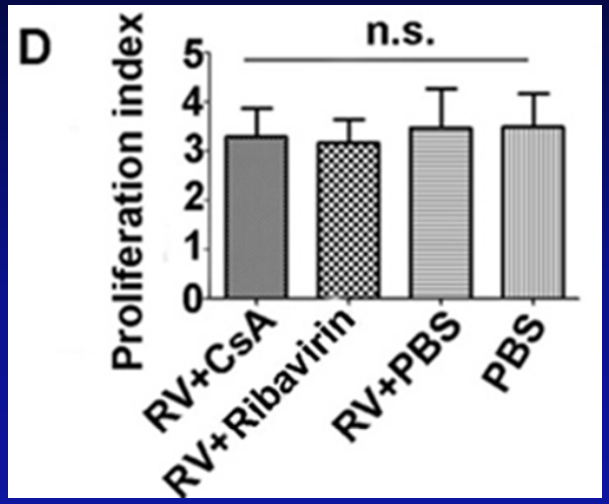
CsA toxicity analysis in the animal model

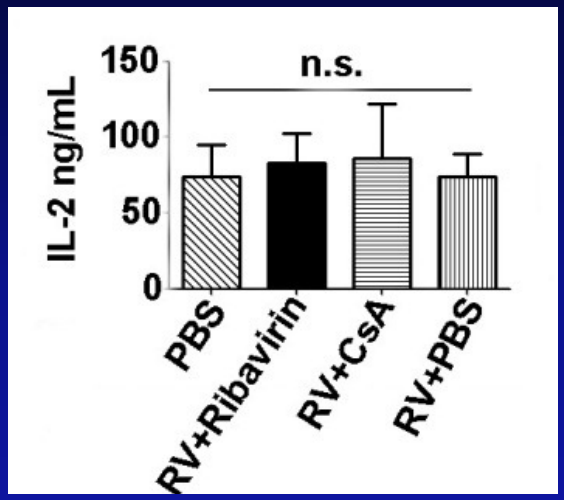


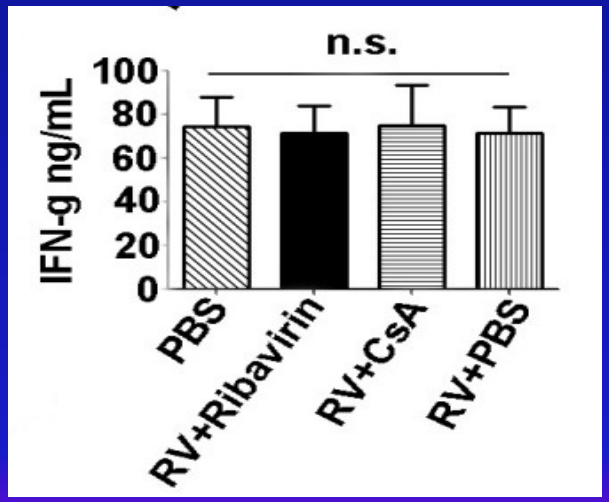
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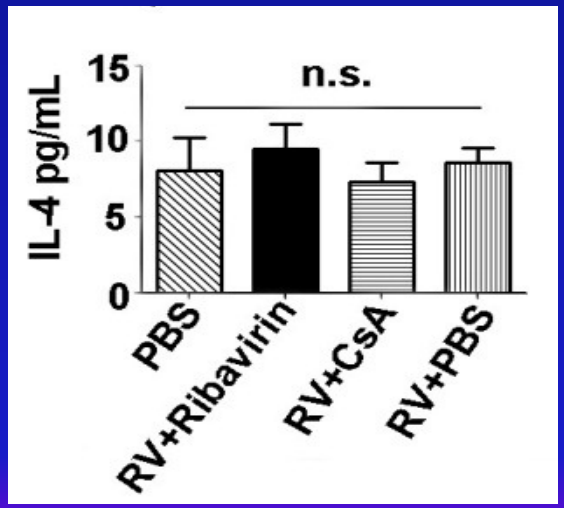


CsA toxicity analysis in the animal model









Conclusions

- CsA treatment of HT-29 cells in vitro suppresses Wa rotavirus infection. Furthermore, CsA inhibited Wa rotavirus replication
- CsA treatment restores IFN-β expression through suppressing Wa rotavirus and its proteins, not IFN-α and/or IFN-β regulatory genes
- CsA promoted Interferon Regulatory Factor-5 (IRF-5) expression, but not IRF-1, IRF-3, or IRF-7. Additionally, CsA inhibited SOCS-1 expression, but not SOCS-2 or SOCS-3

- The antiviral effect of CsA was confirmed in an RV-infected neonatal mouse model by evaluation of antigen clearance and assessment of changes in intestinal tissue pathology
- Also, there was no significant toxicity in the dose range we used in the experiments both in vitro and in vivo. Such as no differences in T cell frequency or proliferation between the CsA- and vehicle-treated groups were observed,
- CsA may be a useful candidate to develop a new anti-RV strategy, although further evaluation and characterization of CsA on RV-induced diarrhea are warranted.

- You are always welcome to ask me any questions once you have

Thank You!



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