

# Transient receptor potential vanilloid type 1 attenuates lung ischemia-reperfusion injury through activation of a7 nicotinic acetylcholine receptor in mice

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## **Background and Goal of Study**

Cholinergic anti-inflammatory pathway is a mechanism that brain regulates inflammation through vagal efferent nerves and  $\alpha$ 7 nicotinic acetylcholine receptors ( $\alpha$ 7nAChR). Our studies indicated that activation of transient receptor potential vanilloid type I (TRPVI) channels expressed on vagal afferent sensory nerves decreased lung ischemia-reperfusion injury (LIRI) in rabbits and rats. This study was designed to detect whether TRPVI attenuated LIRI through  $\alpha$ 7nAChR anti-inflammatory pathway.

### **Materials and methods**

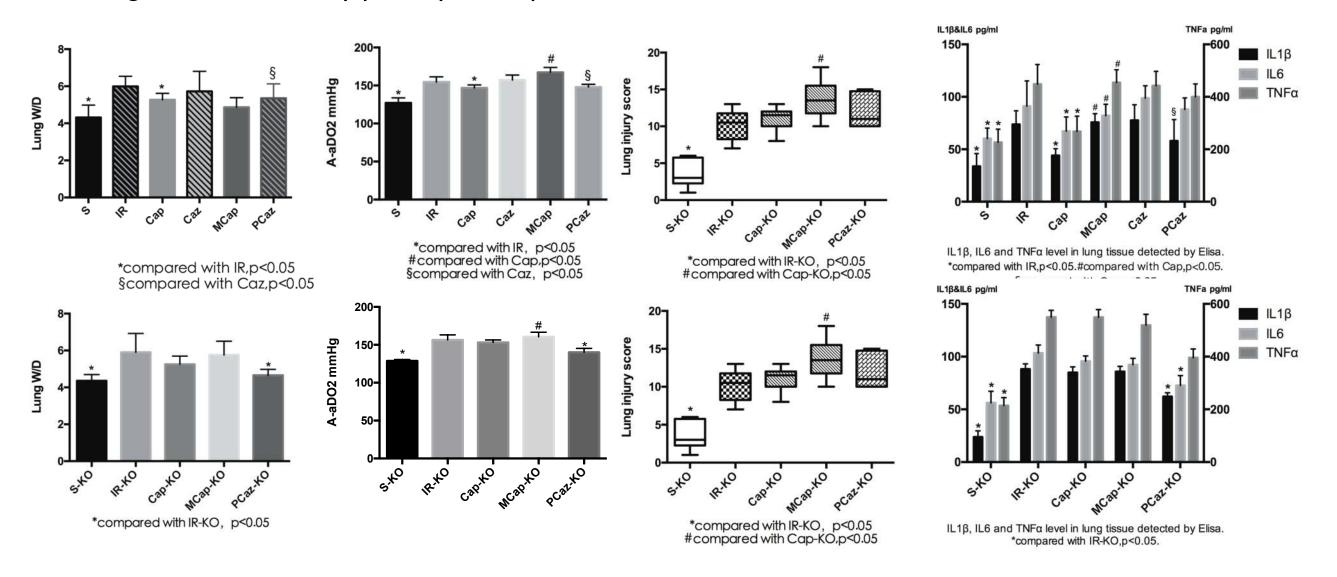
Before Ih of lung ischemia and 2h of reperfusion, wild type (WT) mice or TRPVI knock-out (KO) mice were pretreated with placebo (IR or IR-KO group), TRPVI agonist capsaicin (Cap, Cap or Cap-KO group), TRPVI antagonist capsazepine (Caz)+ Cap (Caz or Caz-KO group), methyllycaconitine (MLA, a  $\alpha$ 7nAChR-selective antagonist) + Cap (MCap or MCap-KO group), or PNU (a  $\alpha$ 7nAChR-selective agonist) + Caz (PCaz or PCaz-KO group), respectively. Sham groups (S or S-KO) were pretreated with vehicles and ventilated for 3h. Blood and lung tissue were obtained for blood gas indexes, lung wet-to-dry (W/D) weight ratio, HE staining for pathologic score, and ILI  $\beta$ , IL6 and TNF $\alpha$  levels in lung tissue.

### **Results and discussion**

I) Cap pretreatment in Cap group resulted in decreased lung W/D ratio, pathologic score, alveolar-arterial oxygen gradient (A-aDO2), and ILI  $\beta$ , IL6 and TNF $\alpha$  (p< 0.05 vs IR), while the reduction disappeared in Caz, Cap-KO and Caz-KO groups (p>0.05 vs IR or IR-KO). These data indicated activation of TRPVI by Cap improved lung inflammation and lung injury, while Caz or TRPVI KO abrogated this improvement in mice. 2) After treated with MLA, MCap group presented higher A-aDO2, pathologic score, and ILI  $\beta$ , IL6 and TNF $\alpha$  levels (p< 0.05 vs Cap). For MCap-KO group, there was a rise in the levels of A-aDO2 and pathologic score (p< 0.05 vs Cap-KO). PCaz group showed lower levels of A-aDO2, pathologic score, W/D ration and ILI  $\beta$  (p< 0.05 vs Caz group). PCaz-KO group showed lower levels of A-aDO2, pathologic score, ILI  $\beta$  and IL6 (p< 0.05 vs IR-KO). Thus, administration of  $\alpha$ 7nAChR antagonist abolished the protective effect of Cap, while agonist generated similar protection even in TRPVI KO mice and WT mice treated with Caz.

#### Conclusion

Activation of TRPVI attenuates LIRI probably through  $\alpha$  7nAChR anti-inflammatory way. The specific role of cholinergic anti-inflammatory pathway in this protection remains to be revealed.



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