Transient receptor potential vanilloid type 1 attenuates lung ischemia-reperfusion injury through activation of α7 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 α7 nicotinic acetylcholine receptors (α7nAChR). Our studies indicated that activation of transient receptor potential vanilloid type 1 (TRPV1) channels expressed on vagal afferent sensory nerves decreased lung ischemia-reperfusion injury (LIRI) in rabbits and rats. This study was designed to detect whether TRPV1 attenuated LIRI through α7nAChR anti-inflammatory pathway.

Materials and methods

Before 1h of lung ischemia and 2h of reperfusion, wild type (WT) mice or TRPV1 knock-out (KO) mice were pretreated with placebo (IR or IR-KO group), TRPV1 agonist capsaicin (Cap, Cap or Cap-KO group), TRPV1 antagonist capsazepine (Caz)+ Cap (Caz or Caz-KO group), methyllycaconitine (MLA, a α7nAChR-selective antagonist) + Cap (MCap or MCap-KO group), or PNU (a α7nAChR-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 IL1β, IL6 and TNFα levels in lung tissue.

Results and discussion

1) Cap pretreatment in Cap group resulted in decreased lung W/D ratio, pathologic score, alveolar-arterial oxygen gradient (A-aDO2), and IL1β, IL6 and TNFα ($p< 0.05$ 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 TRPV1 by Cap improved lung inflammation and lung injury, while Caz or TRPV1 KO abrogated this improvement in mice. 2) After treated with MLA, MCap group presented higher A-aDO2, pathologic score, and IL1β, IL6 and TNFα 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 IL1β ($p< 0.05$ vs Caz group). PCaz-KO group showed lower levels of A-aDO2, pathologic score, IL1β and IL6 ($p< 0.05$ vs IR-KO). Thus, administration of α7nAChR antagonist abolished the protective effect of Cap, while agonist generated similar protection even in TRPV1 KO mice and WT mice treated with Caz.

Conclusion

Activation of TRPV1 attenuates LIRI probably through α7nAChR anti-inflammatory way. The specific role of cholinergic anti-inflammatory pathway in this protection remains to be revealed.