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Poster presentation

Increased ventilatory lung stretch alters the effect of soluble guanylyl cyclase-derived cGMP on endothelial barrier function in isolated mouse lungs

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Background

Ventilator-induced lung injury (VILI) increases lung endothelial permeability. Lung endothelial nitric oxide (NO) generation contributed to this increased permeability in an intact mouse model of VILI [1]. NO stimulates endothelial soluble guanylyl cyclase (sGC) to produce cGMP. The effect of cGMP on endothelial permeability is controversial [2]. We sought to determine 1) if endothelial cGMP is generated in VILI and 2) if changes in endothelial cGMP modulate VILI-induced endothelial barrier dysfunction.

Methods

Isolated C57BL6 mouse lungs (n = 2–6 per group) were ventilated with 21% O_2, 5% CO_2 at a rate of 120 breaths/minute at tidal volumes (TV) of 0, 6, 15 or 20 ml/kg and perfused with a constant flow of physiologic buffer (with 3% albumin). We measured serial perfusate cGMP concentrations (with IBMX) and assessed permeability by the filtration coefficient (Kf; without IBMX). The sGC inhibitor ODQ and the NO-independent sGC activator Bay 41–2272 were used to manipulate sGC activity; atrial natriuretic peptide (ANP) was used to stimulate particulate GC (pGC) activity.

Results

By 80 min of ventilation, perfusate cGMP increased as a function of time and TV with a maximal increase of 24-fold occurring with 15 ml/kg TV. Kf was unchanged with 6 and 15 ml/kg TV (Kf = 0.8 ± 0.3 ml/min/mmHg/100 g) but was increased 6-fold with 20 ml/kg TV indicating VILI. ODQ attenuated cGMP production and eliminated the increased Kf in 20 ml/kg lungs (Kf = 0.8 ± 0.3 ml/min/mmHg/100 g) suggesting sGC/cGMP-mediated barrier dysfunction. Consistent with this, Bay 41–2272 (1.5 μM) administered at 40 min of perfusion further increased perfusate cGMP and markedly exacerbated Kf in 15 ml/kg lungs by 9-fold but neither the low Kf in 6 ml/kg TV lungs nor high Kf in 20 ml/kg TV lungs were affected. The adverse Bay 41–2272 effects on cGMP and Kf could be prevented by ODQ pretreatment ruling out a nonspecific drug effect. Underscoring the apparent injurious interaction of sGC activity and lung stretch, the administration of the same Bay 41–2272 dose 10 min before increasing TV to 15 ml/kg had no effect on Kf after 80 min at this TV (Kf = 1.2 ± 0.5 ml/min/mmHg/100 g) compared to diluent control. Moreover, these effects were specific to sGC, because pGC activation with atrial natriuretic peptide (ANP) did not affect Kf whether administered before or after the onset of injurious ventilation.

Conclusion

These data suggest that endogenous lung endothelial cGMP increases from sGC stimulation in VILI and contributes to VILI-induced endothelial barrier dysfunction. The mechanism of this injurious effect appears to require

an interaction between sGC and lung stretch because 1) an increased level of stretch for a critical period of time was required before sGC activation resulted in endothelial barrier dysfunction and 2) pGC stimulation had no effect. Based on these data we speculate that ventilatory stretch may shift the subcellular location of endothelial sGC to a compartment where cGMP production increases endothelial permeability.

References

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