FPR2/ALX activation reverses LPS-induced vascular hyporeactivity and reduces mortality in pneumosepsis

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Objective: The formylpeptide receptor 2 (FPR2/ALX) is a very promiscuous receptor, utilized by lipid and peptide ligands that trigger pro- or anti-inflammatory responses. FPR2/ALX expression is increased in lung tissues of septic animals and its activation has an effective therapeutic effect by controlling the exacerbated inflammatory response. Although FPR2/ALX expression was observed in vascular smooth muscle cells, its role in vascular reactivity in inflammatory conditions has not been studied. The aim of this study was to investigate the possible role of FPR2/ALX in vascular changes observed during LPS injury and sepsis.

Methods: Rat aorta smooth muscle cell line A7r5 was stimulated with LPS/IFN-γ for 24 h and FPR2/ALX expression was analyzed. Mouse aorta rings were exposed to LPS/IFN-γ in presence or absence of WKYMVm, a FPR2/ALX selective peptide agonist, for 10 h and FPR2/ALX and NOS-2 expression was analyzed. NO production was measured by Griess reaction in A7r5 cells and by DAF-FM probe in aortas. For vascular reactivity studies, each aorta ring preparation was incubated with LPS for 10 h. Then, the preparations were washed several times and a dose-response curve to phenylephrine was obtained. WKYMVm was added concomitantly with LPS for 10 h or 30 min before obtaining phenylephrine response. For survival experiments, WKYMVm or vehicle was injected into mice 2, 14, 26, and 38 h after K. pneumoniae intratracheal instillation and the survival rate was observed every 24 h for 6 days.

Results: LPS increased FPR2/ALX expression in A7r5 cells and aorta rings. WKYMVm reversed LPS-mediated vascular hyporeactivity in aorta rings. Moreover, FPR2/ALX activation by WKYMVm decreased NO production in LPS-stimulated cells and aorta rings, but it did not affect NOS-2 expression. Finally, the treatment of septic animals with WKYMVm improved survival by 40%.

Conclusion: Our data suggest, for the first time, that FPR2/ALX receptor, primarily described as a mediator of immune responses, may have an important role in the vascular dysfunction observed in sepsis and may be a possible target for new therapeutic interventions.

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