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Poster presentation

Is kynurenine a novel and important vasodilator in human septic shock?

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Background

The enzyme indoleamine 2,3-dioxygenase (IDO) converts the amino acid tryptophan (Trp) to kynurenine (Kyn). IDO, which shares many functional similarities with iNOS [1], is also induced in sepsis [2]. Here, we investigated whether IDO plays a role in human septic shock and mouse endotoxemia akin to iNOS.

Materials and methods

Patients (n = 16) with septic shock had IDO activity assessed (expressed as the ratio of Kyn to Trp) and the severity of their hypotension determined (expressed by inotrope requirement) during the course of illness. Normal and blood pressure-matched controls were also studied. Septic shock was induced in wild type and IDO$^{-/-}$ mice, and the effect of 1-methyl-tryptophan (1 MT, a competitive inhibitor of IDO) on blood pressure was determined. In animal studies, IDO expression and activity was assessed by IHC in resistance vessels and plasma Kyn, respectively. The direct vascular effect of Trp and Kyn was determined by vessel functional studies on mouse aortic rings.

Results

Patients' inotrope requirement correlated with IDO activity ($p < 0.001$). IDO activity increased by up to 9-fold with sepsis and was significantly higher than in the two control groups (Figure 1). In mice, endotoxemia led to hypotension, endothelial IDO expression in resistance vessels, and increased IDO activity. In both IDO$^{-/-}$ and the 1MT-pretreated animals, hypotension was attenuated significantly compared to wild-type controls (Figure 2). Similarly, administration of 1 MT to hypotensive mice restored blood pressure to normal. Kyn dose-dependently dilated mouse aortic rings, whereas Trp only dilated arteries from septic mice when IDO was expressed. Trp metabolites of

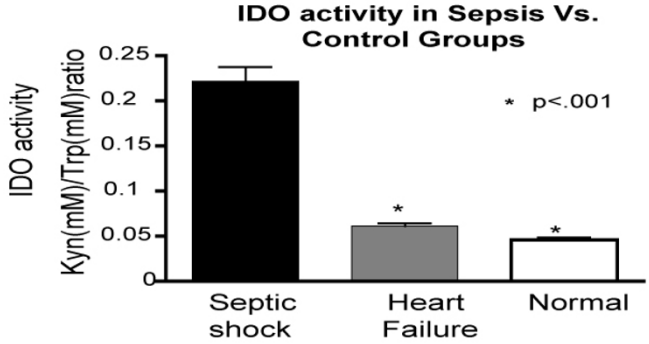

Figure 1
IDO activity in sepsis.

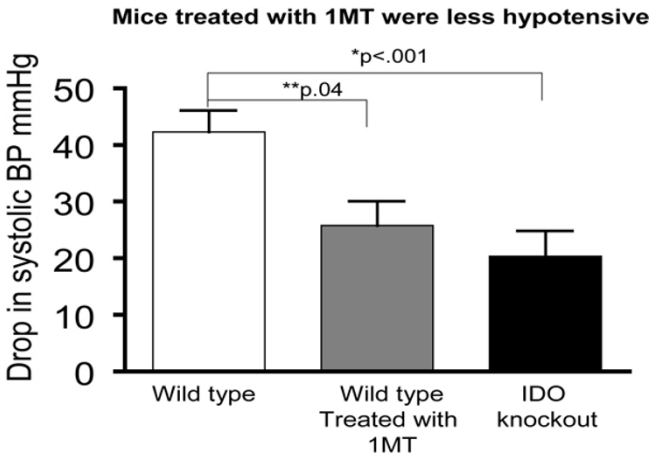

Figure 2
Drop in blood pressure in mice.

the Kyn pathway other than Kyn were not vasoactive. Separate mechanistic studies indicated that Kyn relaxed blood vessels through activation of sGC and adenylate cyclase.

Conclusion

This study shows a significant correlation between IDO activity and hypotension in human septic shock, and that Kyn may act as a previously unrecognized and important vasodilator contributing to hypotension in sepsis. Inhibiting IDO in humans may provide a novel therapeutic target for the treatment of septic shock.

References

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