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Kynurenine is a novel endothelium-derived vascular relaxing factor produced during inflammation

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Background

Control of blood vessel tone is central to vascular homeostasis. Here, we show that metabolism of tryptophan to kynurenine by indoleamine 2,3-dioxygenase (IDO) expressed in endothelial cells contributes to arterial vessel relaxation and the control of blood pressure.

Methods

We used three models of inflammation: infection of mice with malarial parasites (*Plasmodium berghei*), LPS-induced endotoxemia, and transient cerebral ischemia (stroke model). Blood pressure was determined via tail-cuff, and vascular function studies carried out in wire bath systems. IDO expression and activity were assessed by IHC and HPLC, respectively.

Results

All models of inflammation caused expression of IDO in micro-vascular endothelial cells, resulting in decreased plasma tryptophan and increased kynurenine. In malaria infection and endotoxemia, IDO expression was associated with hypotension. Pharmacological inhibition of IDO increased blood pressure in systemically inflamed mice, but not in mice deficient for IDO or interferon-γ, which is required for IDO induction. In endotoxemic mice, IDO deficiency partially attenuated the observed hypotension. In experimental stroke, total infarct volume was similar, yet cortical infarct volume was 4-fold greater in IDO KO than WT mice, consistent with IDO enhancing collateral blood flow. In functional studies, the IDO substrate tryptophan dilated pre-constricted arteries only if active IDO and an intact endothelium were present, whereas the IDO product kynurenine relaxed pre-constricted rings independent of an intact endothelium. Mechanistic studies revealed kynurenine to relax arteries via activation of soluble guanylate cyclase.

Conclusion

This study reveals IDO-mediated tryptophan metabolism to kynurenine as a previously unrecognized and important pathway contributing to the regulation of vascular tone in the setting of inflammation.