The role of endothelin-1 in the vascular pathobiology of cerebral malaria
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Cerebral malaria (CM) is a serious complication of Plasmodium falciparum infection associated with cerebral vasculopathy, high mortality, and risk of neurological sequelae. In human CM, infected RBCs adhere to the brain endothelium and occlude the cerebral blood vessels causing cerebral vascular damage, impaired perfusion, vasospasms, vasoconstriction, and inflammation. Vasoactive factors, including endothelin (ET-1), have become increasingly important in the pathogenesis of CM. We previously demonstrated that antagonism of the ET-1 type A receptor (ETA) improved survival and attenuated brain hemorrhage in murine CM. In this study we tested the hypothesis that ET-1 contributes to CNS inflammation and BBB disruption in experimental CM (ECM) via its actions on ETA. To test this hypothesis we used our model of Plasmodium berghei ANKA (PbA) infection of C57BL/6 mice. PbA-infection resulted in activation of monocyctic CNS cells, microglia, which are important in inflammation. ECM was also associated with an increase in brain microvascular endothelial cell activation which is critical for leukocyte adhesion. Treatment of PbA-infected mice with ETA receptor antagonists attenuated the increase in microglial and endothelial cell activation, suggesting that ET-1 contributes to CNS inflammation during ECM. Furthermore, leakage of Evans blue bound-albumin into the brain was reduced in ECM mice receiving ETA receptor antagonism, providing further support that disruption of the BBB and inflammation during ECM result, in part, from increases in ET-1 and its actions on the ETA receptor. Together these findings illustrate a role for ET-1 in the immunopathology and vasculopathy associated with ECM, and highlight the peptide as a potential target for adjunctive therapy for the protection of neurological function in patients with CM.


Dual endothelin blockade exacerabtes upregulated VEGF angiogenic signaling in the heart of a lipopolysaccharide-induced endotoxemic rat model
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Purpose: Endothelin-1 (ET-1) is overexpressed in breast cancers, while circulating levels of its precursor (Big ET-1) have also been found elevated. In the present study, we evaluated plasma ET-1...