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Research Report

Endothelin-1-mediated vasoconstriction alters cerebral gene expression in iron homeostasis and eicosanoid metabolism

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ABSTRACT

Endothelins are potent vasoconstrictors and signaling molecules. Their effects are broad, impacting processes ranging from neurovascular and cardiovascular health to cell migration and survival. In stroke, traumatic brain injury or subarachnoid hemorrhage, endothelin-1 (ET-1) is induced resulting in cerebral vasospasm, ischemia, reperfusion and the activation of various pathways. Given the central role that ET-1 plays in these patients and to identify the downstream molecular events specific to transient vasoconstriction, we studied the consequences of ET-1-mediated vasoconstriction of the middle cerebral artery in a rat model. Our observations demonstrate that ET-1 can lead to increases in gene expression, including genes associated with the inflammatory response (*Ifnb*, *Il6*, *Tnf*) and oxidative stress (*Hif1a*, *Myc*, *Sod2*). We also observed inductions (>2 fold) of genes involved in eicosanoid biosynthesis (*Pla2g4a*, *Pla2g4b*, *Ptgs2*, *Ptgis*, *Alox12*, *Alox15*), heme metabolism (*Hpx*, *Hmox1*, *Prdx1*) and iron homeostasis (*Hamp*, *Tf*). Our findings demonstrate that mRNA levels for the hormone hepcidin (*Hamp*) are induced in the brain in response to ET-1, providing a novel target in the treatment of multiple conditions. These changes on the ipsilateral side were also accompanied by corresponding changes in a subset of genes in the contralateral hemisphere. Understanding ET-1-mediated events at the molecular level may lead to better treatments for neurological diseases and provide significant impact on neurological function, morbidity and mortality.

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1. Introduction

Endothelins are potent endothelium-derived signaling molecules involved in regulating vascular tone. Three endothelins (ET-1, ET-2 and ET-3) are synthesized as preproendothelin molecules which are cleaved by endothelin converting enzymes into their active forms. Mature endothelins signal through interaction with G-protein coupled receptors ET_A and ET_B (Barton and Yanagisawa, 2008; Masaki, 2004). Stimulation of the vascular endothelium by angiotensin II, antidiuretic hormone, thrombin, cytokines, reactive oxygen species and shearing forces lead to the synthesis and release of ET-1, whereas prostacyclin, atrial natriuretic peptide and nitric oxide inhibit ET-1 release (Stow et al., 2011). The effects of endothelins on the neurovasculature are implicated in a wide range of neurological pathologies including subarachnoid hemorrhage (SAH) (Lin et al., 2004; Sehba and Friedrich, 2013; Suzuki et al., 1992), traumatic brain injury (TBI) (Petrov et al., 2002; Petrov, 2009), Alzheimer's disease (Luo and Grammas, 2010; Palmer et al., 2012) and stroke (Madden, 2012).

Specifically, previous animal studies have concluded that ET is a major initiating component of SAH-mediated vasospasm (Nishizawa et al., 2000; Roux et al., 1995; Suzuki et al., 1992) and that SAH patients have elevated cerebrospinal fluid levels of ET-1 and ET-3 (Fassbender et al., 2000; Pluta et al., 1997). Furthermore, endothelin receptor antagonists have recently been shown to significantly reduce vasospasm-related morbidity in post-SAH patients (Macdonald et al., 2012). Similarly, ET-1 levels are elevated in the CSF and plasma of TBI patients potentially contributing to secondary ischemia and vasogenic edema (Chatfield et al., 2011; Salonia et al., 2010). In Alzheimer's disease, ET-1 mRNA and protein levels are elevated in the neurons and cerebral blood vessels of the temporal cortex, possibly in response to oligomeric

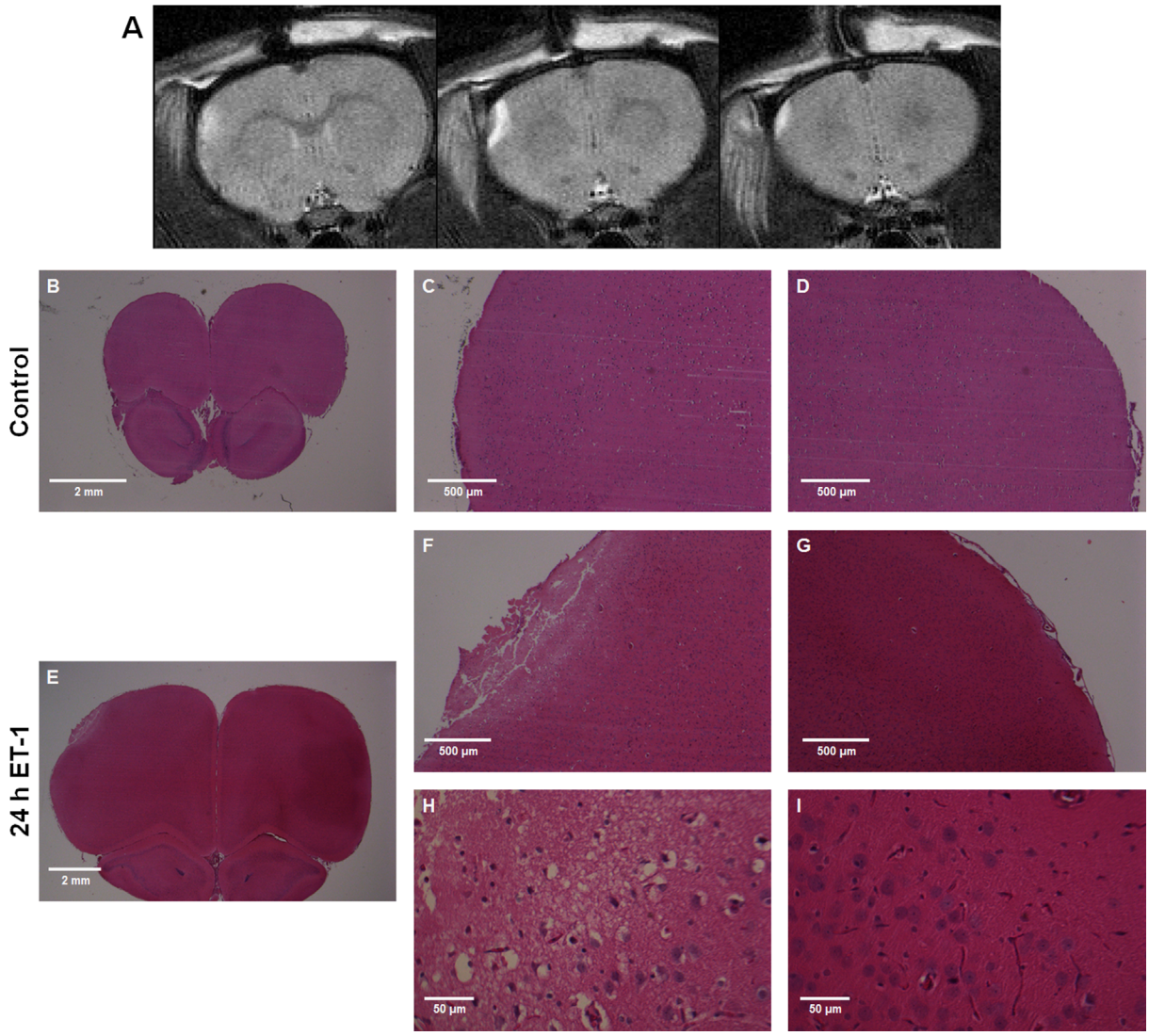

Fig. 1 – MRI and histological assessment ET-1-mediated vasoconstriction. (A) T2-weighted MRI of adjacent 1 mm sections shows the size and extent of damage following ET-1 treatment. (B–D) Hematoxylin and eosin staining of control brain slices from each hemisphere. (E–I) Hematoxylin and eosin staining at 24 h post-ET-1-mediated vasoconstriction on the (F, H) ipsilateral and (G, I) contralateral hemispheres demonstrating damage and microvacuolization.