Loss of Bax-interacting factor-1 increases neuronal sensitivity to ischemic injury

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Bax-interacting factor-1 (Bif-1) is a multifunctional protein involved in the regulation of apoptosis, autophagy and mitochondrial function. Previous studies in non-neuronal cells have shown that Bif-1 is pro-apoptotic and promotes mitochondrial fragmentation. We recently described neuron-specific alternatively spliced isoforms of Bif-1 that confer neuroprotection. During ischemic stroke, expression of neuron-specific Bif-1 isoforms was selectively downregulated in the penumbra of wild-type mice. Consistent with Bif-1 being required for neuronal viability, Bif-1-deficient mice developed larger infarcts and an exaggerated astrogliosis response following ischemic stroke. To further establish a direct role for Bif-1 in the neuronal response to ischemia we evaluated ischemic injury in primary cortical neurons in culture. As little as two hours of hypoxia (1%) in the absence of reperfusion was sufficient to promote neuronal apoptosis. Bif-1 knockdown significantly increased cell death in response to hypoxia alone. The neuron-specific form of Bif-1 was not reduced in response to hypoxia alone in normal medium or in medium depleted of glucose and the B27 supplement (depleted medium). However, hypoxia (in depleted medium) and reperfusion resulted in a marked reduction in neuron-specific Bif-1, similar to the changes observed in vivo with middle cerebral artery occlusion. Importantly, overexpression of neuron-specific Bif-1c reduced cell death induced by hypoxia/reperfusion. This finding not only demonstrates an unexpected role for Bif-1 in the nervous system but this work also establishes Bif-1 as a potential therapeutic target for the treatment of brain injury.