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Neuroprotection by insulin and glucagon: Role of glutamate

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Acute ischemic stroke (AIS) increases brain glutamate and tPA, which exacerbates neurologic impairment by activating N-Methyl-D-aspartate receptors (NMDARs). We reported that glucagon(J Neurosurg. 2011;114:85 & Journal of Neurotrauma. 2011;28:451) and insulin (Am J of Physiol - Regul, Integr and Comp Physiol. 2011; 301: R668) provide comparable neuroprotection in normal pigs(Neurotrauma. 2011;28:451) and in normal and diabetic rats in models of AIS (Am J of Physiol - Regul, Integr and Comp Physiol. 2011; 301: R668) and traumatic brain injury (TBI)(J Neurosurg. 2011;114:85) by reducing cerebral glutamate, although they have opposing effects on blood glucose (J Neurosurg. 2011;114:85 & J Neurosurg. 2011;114:85). Both hormones decrease blood and CSF glutamate to the same extent and they exhibit similar therapeutic windows that overlap with the period when glutamate is elevated in the CSF after AIS or TBI(J Neurosurg. 2011;114:85 & J Neurosurg. 2011;114:85).

Activation of NMDARs has both vital and neurotoxic effects, but the mechanism by which this transition occurs is uncertain. New data suggest NMDARs activate two opposing intracellular pathways that depend on the subunit composition of the NMDARs and their intracellular adaptors that regulate neuronal cAMP and cell viability. We found that glucagon prevents the fall in cAMP, inactivation of PKA and increases in TNFα and IL-1β that occurs post AIS. Inhibiting the activity of PI3K or phosphodiesterase 4 (PDE4) mimics the effect of glucagon on preserving cAMP levels and neuroprotection. Inhibition of glucagon release by somatostatin (SOMAT) increases CSF glutamate and brain damage induced by AIS, indicating that endogenous glucagon is neuroprotective as well.

We also found that $tPA^{-/-}$ mice are resistant to neuroprotection by glucagon and deleterious effects of SOMAT because they are resistant to neurotoxicity by glutamate, which indicates that injury is tPA dependent. Moreover, tPA is not neurotoxic in the absence of glutamate, suggesting that glucagon also prevents the neurotoxicity of endogenous tPA released post AIS by decreasing glutamate. Based on our finding that the neurotoxicity of glutamate is tPA dependent, we will explored new approaches to mimic the neuroprotection of glucagon by neutralizing the activation of NMDARs by endogenous tPA using deletion mutants of tPA that can't bind or activate the receptor.

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