DMT1−dependent neurodegeneration: a novel target to develop anti-ischemic drugs by reducing ferrous iron uptake

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The molecular mechanisms that link iron overload and neurodegenerative features in brain ischemia are an intensively investigated area that could give rise to novel therapeutic approaches. We have demonstrated that increased expression of the 1B isoform of the divalent metal transporter 1 without iron-response-element [1B/(-)IRE DMT1] is an early response to NF-kB/RelA activation through Lys310 acetylation during brain ischemia (Ingrassia et al., 2012). We showed that either oxygen−glucose−deprivation (OGD) or over−expression of 1B/(−)IRE DMT1 isoform significantly increased iron uptake, as detected by total reflection X−ray fluorescence, and iron−dependent cell death in neuronally differentiated SK−N−SH cells. Iron chelation by deferoxamine treatment or (−)IRE DMT1 RNA silencing significantly prevented OGD-mediated neuronal with a concomitant decrease of intracellular iron levels. Moreover, we have previously demonstrated that leptin, the adipose hormone that regulates food intake and energy expenditure, was able to reduce ischemic brain injury through an NF−kB/c−Rel−dependent mechanism, both in vitro and in vivo (Valerio et al., 2009). Notably, the pancreatic ß cell−conditional DMT1 knockout mice have been recently described with reduced blood glucose levels and concomitant increased insulin secretion, and with ß cell protection from cytokine−induced apoptosis when the mice were fed a high−fat diet (Hansen et al, 2012). Since leptin and insulin partly share downstream signaling pathways and can activate Sirtuin1 (Liu et al, 2013), the histone deacetylase which suppresses NF-kB/RelA transcriptional activity through Lys310 deacetylation (Yeung et al., 2004), we hypothesized that a regulatory effect on DMT1 by leptin/insulin may exist in neurons. Thus, we performed in vitro experiments which show that leptin and insulin are able to promote neuroprotection during both OGD and acute ferrous iron overload in neuronally differentiated SK−N−SH cells, with concomitatnt down-regulation of DMT1. Moreover, we found that Sirt1 overexpression significantly protects neurons from death induced by an acute ferrous iron treatment, possibly through DMT1 down-regulation. Further experiments are in progress to establish the influence of leptin and insulin on DMT1 during neuronal ischemia.

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