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The effects of 6-OHDA on iron metabolism in astrocytes are mediated by hypoxia-inducible factors

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Disrupted iron homeostasis in the substantia nigra (SN) is involved in Parkinson's disease (PD). When loaded with iron, neurons and microglia die, but astrocytes have a high iron tolerance and can proliferate in the same situation. Our previous studies have shown that in astrocytes, expression of divalent metal transporter 1 (DMT1) and iron export protein ferroportin1 (FPN1) are both upregulated after 6-hydroxydopamine (6-OHDA) treatment, but the mechanisms remain unclear. Hypoxia-inducible factors (HIFs) are known to be important in regulating iron homeostasis. Binding of HIF-2α to the promoter region of the hypoxia response elements (HREs) of DMT1 and FPN1 increases their expression. However, as yet it is unclear if HIFs are involved in the regulation of DMT1 and FPN1 expression in astrocytes treated with 6-OHDA.Using western blots, we observed HIFs, DMT1 and FPN1 expressions in primary cultured astrocytes and SH-SY5Y neuron cell lines treated with 6-OHDA, inhibitors of HIF-1α and HIF-2α, protein kinase C (PKC) inhibitor and PKC activator, radical scavenger and inducible NO synthase (iNOS) inhibitor. The ferrous iron traffic of astrocytes was determined by measuring the quenching or reversing of calcein fluorescence. In this study, we found that protein levels of HIF-1α and HIF-2α in astrocytes were significantly increased by treatment with 6-OHDA, whereas expression did not change in dopaminergic neurons. Furthermore, using inhibitors of HIF-1α and HIF-2α, we observed that an HIF-2α inhibitor markedly reduced the up-regulation of DMT1 and FPN1 by 6-OHDA and decreased ferrous iron influx and efflux. However, there was no effect following treatment of astrocytes with the HIF-1α inhibitor. We found that PMA activated HIF-2α, leading to increased expression of DMT1 and FPN1. Activation of HIF-2α by PMA and 6-OHDA was blocked by Bisl preventing downstream activation of DMT1 and FPN1. Likewise, N-acetyl-l-cysteine (NAC) or Nω-Nitro-L-arginine methyl ester hydrochloride (L-NAME) were found to block HIF-2α activation by 6-OHDA. Our data indicate that HIF-2α, but not HIF-1α, regulates expression of DMT1 and FPN1 in astrocytes. Furthermore, we conclude that PKC pathway, reactive oxygen species (ROS) and reactive nitrogen species (RNS) were involved in HIF-2α activation.

Biography

Jun Wang completed her PhD from Qingdao University and Post-doctorate from the University at Buffalo, USA. She is a Professor at the Department of Physiology and Pathophysiology in Qingdao University. She has published more than 30 papers in reputed journals.

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