Epigenetic modifications associated with selective neuronal vulnerability in a rat model of transient global brain ischemia

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Epigenetics refers to a complex of stable and heritable molecular processes that dynamically modulate gene expression and function without any change in the nucleotide sequence. Epigenetic phenomena are mediated by a variety of molecular mechanisms including DNA methylation and histone acetylation, methylation and phosphorylation associated with chromatin remodeling. Aberrant epigenetic mechanisms have been associated with a variety of human disorders including atherosclerosis, insulin resistance, obesity, and with vascular risk factors for stroke. Moreover, emerging evidence suggests that epigenetic processes play a critical role in shaping neuronal vulnerability to an ischemic insult, and influence the progression of ischemic neuronal damage as well as the functional recovery after stroke. If so, the study of the epigenetic events that drive the pathological gene programming associated with brain ischemia may lead to the identification of new targets for 'pathogenetic' drugs of potential use in the treatment of stroke. In order to characterize some of the epigenetic events associated with delayed neuronal death we used the 4-vessel occlusion (4VO) model of transient global ischemia in rats. This model provides a well- established model of neuronal insult in which cell death occurs primarily in CA1 pyramidal neurons and is delayed by 3-4 days, whereas neurons of the CA3 region are relatively protected. In the present study we focused on the expression analysis of enzymes and co-factors involved in epigenetic mechanisms, such as DNA-methyltransferases (DNMTs), histone deacetylases (HDACs), MeCP2, GADD45β and APOBEC in CA1 and CA3 regions at different time that precede neuronal death following ischemia/reperfusion (6, 12 and 24 hours). Notably, we found that global ischemia was able to induce a substantial and CA1 specific increase in DNMT3a and HDAC2 expression at 12 hours after reperfusion. HDAC3 and GADD45β expression was increased both in CA1 and CA3 regions. No changes in MeCP2 and APOBEC expression were detected. We are currently examining the potential gene targets that are negatively regulated by HDAC2 and DNMT3a in relation to neuronal vulnerability after transient ischemia.