Genomic and non-genomic regulation of PGC1 isoforms by estrogen to increase cerebral vascular mitochondrial biogenesis and reactive oxygen species protection

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Résumé en anglais	We previously found that estrogen exerts a novel protective effect on mitochondria in brain vasculature. Here we demonstrate in rat cerebral blood vessels that 17beta-estradiol (estrogen), both in vivo and ex vivo, affects key transcriptional coactivators responsible for mitochondrial regulation. Treatment of ovariectomized rats with estrogen in vivo lowered mRNA levels of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1alpha) but increased levels of the other PGC-1 isoforms: PGC-1beta and PGC-1 related coactivator (PRC). In vessels ex vivo, estrogen decreased protein levels of PGC-1alpha via activation of phosphatidylinositol 3-kinase (PI3K). Estrogen treatment also increased phosphorylation of forkhead transcription factor, FoxO1, a known pathway for PGC-1alpha downregulation. In contrast to the decrease in PGC-1alpha, estrogen increased protein levels of nuclear respiratory factor 1, a known PGC target and mediator of mitochondrial biogenesis. The latter effect of estrogen was independent of PI3K, suggesting a separate mechanism consistent with increased expression of PGC-1beta and PRC. We demonstrated increased mitochondrial biogenesis following estrogen treatment in vivo; cerebrovascular levels of mitochondrial transcription factor A and electron transport chain subunits as well as the mitochondrial/nuclear DNA ratio were increased. We examined a downstream target of PGC-1beta, glutamate-cysteine ligase (GCL), the rate-limiting enzyme for glutathione synthesis. In vivo estrogen increased protein levels of both GCL subunits and total glutathione levels. Together these data show estrogen differentially regulates PGC-1 isoforms in brain vasculature, underscoring the importance of these coactivators in adapting mitochondria in specific tissues. By upregulating PGC-1beta and/or PRC, estrogen appears to enhance mitochondrial biogenesis, function and reactive oxygen species protection.
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