Protein Kinase G mediates neuroprotective effects of PDE2A inhibition on mitochondria by phosphorylating DLP1 at S637

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The spatial and temporal signaling by second messengers cAMP and cGMP are tightly regulated by phosphodiesterase enzymes that degrade cyclic nucleotides. PDE2A is the major phosphodiesterase expressed in the hippocampus and frontal/temporal cortex where it regulates memory and cognitive function. Recent studies demonstrated that inhibition of PDE2A leads to mitochondrial elongation and neuroprotection, presumably by enhancing cAMP/PKA-dependent phosphorylation of DLP1. However, as PDE2 also modulates cGMP levels and PKG activity, it remains to be determined whether cGMP/PKG is involved in PDE2-dpendent regulation of mitochondrial morphology. In this regard, bioinformatic analysis revealed that PKA and PKG share the same consensus site on DLP1 (S637). In vitro kinase assay confirmed the direct phosphorylation of DLP1 by PKG. Direct interaction between PKG and DLP1 was confirmed by co-immunoprecipitation after overexpression of PKG and DLP1 in M17 cells. Overexpression of PKG and DLP1 in HEK293T cells led to a robust increase in pS637 DLP1 levels. Moreover, the selective PKG activator, 8-Br-cGMP, induces increased pS637 of endogenous DLP1 as well as mitochondrial elongation in the M17 neuroblastoma cell line. More importantly, PKG inhibitor KT5823, similar to PKA inhibitor H89, partially blocked the rescuing effect of Bay 60-7550, an inhibitor of PDE2A, on PDE2A overexpression-induced mitochondrial dysfunction and morphology. Taken together, these results demonstrate that PKG phosphorylates DLP1 at Ser637 and that the cGMP-PKG-DLP1 axis is one mechanism via which PDE2A inhibition exerts its neuroprotective effects.

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