The stability of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase–3 (Pfkfb3), a master regulator of glycolysis, determines the survival of post-mitotic neurons.

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6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase (Pfkfb) catalyzes the formation and degradation of fructose-2,6-bisphosphate, the most potent alosteric activator of 6-phosphofructo-1-kinase –a major regulator of the glycolytic pathway. Recently, we found that nitric oxide exerts a fine, fast and strong stimulation of glycolysis –and cytoprotection– through the alosteric activation of Pfkfb, brain isoform (Pfkfb3), in cultured astrocytes (1). We have now investigated whether the control of glycolysis by Pfkfb3 would dictate neuronal survival. Western blot analyses, using a Pfkfb3 specific antibody that we developed, revealed that Pfkfb3 protein was profusely expressed in astrocytes, whereas it was undetectable in terminally differentiated neurons. Thus, during *in vitro* neuronal differentiation, Pfkfb3 protein disappeared progressively, whereas its mRNA was present throughout the full differentiation process. Incubation of post-mitotic neurons with inhibitors of the proteasome rapidly induced Pfkfb3 protein accumulation. Moreover, over-expression of Pfkfb3 prevented apoptotic death during terminal neuronal differentiation. Thus, the control of Pfkfb3 protein stability by the ubiquitin-proteasome pathway dictates neuronal survival. This may be relevant for understanding the mechanisms responsible for the high vulnerability of neurons against mitochondrial damage in neurodegenerative diseases.

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**References**

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