Ganglioside GM3 is involved in neuronal cell death

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Gangliosides abundant in the nervous system have been implicated in a broad range of biological functions, including the regulation of cell proliferation and death. Glutamate-induced cell death, which is accompanied by an accumulation of reactive oxygen species (ROS), is a major contributor to pathological cell death within the nervous system. However, the mechanism underlying this neuronal cell death has not been fully elucidated. In this study, we report that ganglioside GM3 is involved in neuronal cell death. GM3 was up-regulated in the mouse hippocampal cell line HT22 death caused by glutamate. Increment in GM3 levels by both the exogenous addition of GM3 and the overexpression of the GM3 synthase gene induced neuronal cell death. Overexpression of GM3 synthase by microinjecting mRNA into zebrafish embryos resulted in neuronal cell death in the central nervous system (CNS). Conversely, RNA interferencemediated silencing of GM3 synthase rescued glutamateinduced neuronal death, as evidenced by the inhibition of massive ROS production and intracellular calcium ion influx. 12-lipoxygenase (12-lipoxygenase) (12-LOX) was recruited to glycosphingolipid-enriched microdomains (GEM) in a GM3-dependent manner during oxidative glutamate toxicity. Our findings suggest that GM3 acts as not only a mediator of oxidative HT22 death by glutamate but also a modulator of in vivo neuronal cell death. - *FASEB J.* (2006).

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