

## **Methylmercury Toxicity Is Induced by Elevation of Intracellular Ca<sup>2+</sup> through Activation of Phosphatidylcholine-Specific Phospholipase C**

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Methylmercury (MeHg) is a ubiquitous environmental toxicant that can be exposed to humans by ingestion of contaminated food including fish and bread. MeHg has been suggested to exert its toxicity through its high reactivity to thiols, generation of arachidonic acid and reactive oxygen species (ROS), and elevation of intracellular Ca<sup>2+</sup> levels ([Ca<sup>2+</sup>]<sub>i</sub>). However, the precise mechanism has not been fully defined. Here we show that phosphatidylcholine-specific phospholipase C (PC-PLC) is a critical pathway for MeHg-induced toxicity. MeHg activated the acidic form of sphingomyelinase (A-SMase) and group IV cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>) downstream of PC-PLC, but these enzymes as well as protein kinase C were not linked to MeHg's toxicity. Furthermore, MeHg produced ROS, which did not cause the toxicity. However, D609, an inhibitor of PC-PLC, significantly reversed the toxicity in a time- and dose-dependent manner in MDCK and SH-5YSY cells. Addition of EGTA to culture media resulted in partial decrease of [Ca<sup>2+</sup>]<sub>i</sub> and partially blocked cell death. In contrast, D609 completely prevented cell death with parallel decreases in diacylglycerol and [Ca<sup>2+</sup>]<sub>i</sub>. Together, our findings indicated that MeHg-induced toxicity was caused by elevation of [Ca<sup>2+</sup>]<sub>i</sub> through activation of PC-PLC. The toxicity was not attributable to the signaling pathways such as cPLA<sub>2</sub>, A-SMase, and PKC, or to the generation of ROS.