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MeHg-induced ceramide generation by the activation of acid form of sphingomyelinase in MDCK cells

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Methyl mercury (MeHg) is the most important form of mercury in terms of toxicity and health effects from envionmental exposure. If taken up by fish in the foodchains, it is highly concentrated to humans. MeHg-poisoned animals exhibit typical neurological symptoms, pathological changes in the kidney, and liver. But the biological, molecular mechanisms responsible for the toxicity of MeHg are still poorly understood.

MeHg induced the generation of ceramide in concomitant with SM hydrolysis. It is likely that activation of A-SMase is responsible for MeHg-indcued ceramide generation since Monensin or NH_4Cl, the indirect inhibitor for A-SMase, inhibited the ceramide generation. Moreover, it seems that A-SMase, not N-SMase, is markedly activated by MeHg. The ceramide generation through SM hydrolysis pathway is further supported in that the pretreatment of cells with Fumonisin B_1, a ceramide synthase inhibitor, can't influence MeHg-induced ceramide level changes. D609, a specific inhibitor of PC-PLC, inhibited the MeHg-induced DAG generation, A-SMase activation, and ceramide generation. Interestingly, D609 also protected against the cytotoxicity of MeHg.

Moreover, MeHg induced Arachidonic acid (AA) release and intracellular ROS generation, which are blocked by pretreatment of $AACOCF_3$, a specific inhibitor of $cPLA_2$. It was suggested that MeHg stimulated AA release leading to intracellular ROS generation.

In summary, MeHg-induced cytotoxicity may be due to ceamide generation through the sequential activation of PC-PLC, A-SMase or the combined effects on multiple pathways including release of AA, production of intracellular ROS.