sphingoid bases. Clinical use of paclitaxel may maximize its cytotoxic potential through its ceramide-producing activity.

[PA4-15] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Ceramide Is Linked to Glutamate-induced Cell Death in Cultured Cortical Neurons

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Glutamate is known to play a pivotal role in the pathogenesis of epileptic seizure, brain injury associated with stroke and trauma as well as in neurodegenerative disease such as Alzheimer's disease, Huntington's chorea and Parkinson's disease. While excessive activation of glutamate receptor is responsible for neuronal injury, glutamate has, recently, been known to induce apoptosis in cultured rat neocortical neurons. Thus far, overstimulation of glutamate receptors has been known to induce intracellular calcium overload, which activates a cascade of cytotoxic biochemical events leading to necrotic neuronal death. However, the mechanism by which glutamate induce such neuronal apoptosis has not been fully understood. Here we for the first time report that ceramide was increased by treatment of glutamate to the primary cortical neurons with a concomitant decrease in sphingomyelin and may be responsible for the neuronal apoptosis. The cortical neurons contain a neutral form of N-SMase as a major SMase activity, whose activity was rapidly and stably enhanced by glutamate. Furthermore, MK801, an antagonist of glutamate receptor, significantly blocked these biochemical and cellular events. Our data suggest that glutamate-induced neuronal apoptosis could be provoked by ceramide produced through activation of a neutral form of N-SMase.

[PA4-16] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Phosphatidylcholine-specific Phospholipase C-mediated Activation of Acidic Form of Sphingomyelinase May Lead to Methylmercury-induced Cell Death

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Methylmercury (CH_3HgCl) is the most important form of mercury in terms of toxicity and health because of its high level of bioconcentration through aquatic food chains. Although this compound has been known to affect various organs including brain and kidney, the mechanism remains poorly understood. In this work, the biochemical events associated with cell death induced by CH_3HgCl have been analyzed in Madin Darby Cannine Kidney (MDCK) cells. Results indicate that CH_3HgCl-induced cell death is attributable to an early ceramide generation caused by the activation of an acidic spingomyelinase (A-SMase). Moreover CH_3HgCl treatment rapidly induces diacylglycerol (DAG) generation through activation of phosphatidylcholine-specific phospholipase C (PC-PLC), an event which preceeds and is required for A-SMase activation. Moreover A-SMase activity, but not neutral form of SMase, was stably enhanced by exposing MDCK cells to CH_3HgCl. Indeed, PC-PLC inhibition by D609 totally prevented CH_3HgCl-induced A-SMase activity, ceramide generation and consequent cell death. These observations indicate that CH_3HgCl induces MDCK cell death through the sequential activation of PC-PLC and A-SMase, and early ceramide generation.

[PA4-17] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]