Title

Thimerosal-Induced Neuritoxicity: Apoptosis Occurs Through A Mitochondrial-Mediated Pathway Via the JNK Signaling Pathway (https://mds.marshall.edu/cgi/viewcontent.cgi?article=1640&context=etd)

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Abstract

Thimerosal is an organic mercurial containing an ethylmercury moiety attached to the sulfur atom of thiosalicylate. Since the 1930s, thimerosal has been used as an antiseptic and a preservative in a wide variety of products, including medicinal preparations administered to children and pregnant women. Past exposures to mercurials have indicated that mercury is a neurotoxin, and can also affect the kidney, skin, eyes, and immune system. Additionally, fetuses exposed to mercurials are more susceptible to toxicity because the nervous system is continuously developing. However, despite its widespread use, thimerosal was only studied on a limited basis until the end of the 1990s. At that time, the use of thimerosal in vaccines began to concern parents and physicians because of its potential neurotoxicity, creating a controversy surrounding the question of safety. Consequently, studies with cell culture and animal models have begun to discern the mechanisms of toxicity of thimerosal. The present study hypothesized that thimerosal-induced toxicity occurs through the cJun N-terminal kinase (JNK)/Activator Protein-1 (AP-1) pathway. We used a human neuroblastoma cell line (SK-N-SH) as a model for neurotoxicity because it has characteristics that resemble the developing nervous system. SK-N-SH cells treated with thimerosal underwent apoptosis in a mitochondrial-dependent manner, as demonstrated by release of cytochrome *c*, activation of caspases 9 and 3, degradation of poly(ADP)-ribose polymerase (PARP), DNA condensation and fragmentation, along with release of lactate dehydrogenase (LDH), which occurs late in apoptosis. Thimerosal-treated cells also showed activation of the JNK pathway through increases in phosphorylation of JNK and cJun. However, despite increases in AP-1 transcriptional activity, use of a dominant negative to cJun (TAM67) showed that AP-1 activation is not essential to thimerosal- induced apoptosis. Use of a cell permeable JNK inhibitor (SP600125) demonstrated that JNK activation is a necessary component of thimerosal-induced apoptosis. An additional component of thimerosal toxicity is an increase in oxidative stress. Antioxidants were used to determine if the oxidative stress component was connected to the JNK pathway activation. The antioxidant Trolox and the glutathione precursor N- acetylcysteine (NAC) both protected the cells from apoptosis, but served to increase the phosphorylation of JNK, while still decreasing levels of the proapoptotic protein Bim. Additionally, the JNK inhibitor decreased levels of the stress-response protein heme oxygenase-1 (HO-1). These results indicate that while the oxidative stress pathway and the JNK pathway may be affected by the actions of the other, additional intermediates are involved. Taken together, these results present a significant increase in the cumulative information concerning the mechanism of thimerosal-induced neurotoxicity. By increasing the overall knowledge base, we provide targets for the development of methods to attenuate potential neurotoxicity in patients exposed to thimerosal.

Subject(s)

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Apoptosis.

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