Journal of Andrology, Vol 17, Issue 5 538-549, Copyright © 1996 by The American Society of Andrology

JOURNAL ARTICLE

2-Methoxyacetic acid (MAA)-induced spermatocyte apoptosis in human and rat testes: an in vitro comparison

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2-Methoxyethanol (2-ME) produces adverse reproductive effects in humans at an exposure level that is about 60-fold lower (2.6 mg/m3) than the concentration toxic to rat testes (167 mg/m3), suggesting that humans are much more sensitive to the testicular toxicity of 2-ME than rats. Previous studies found that 2-ME-induced germ cell death seen in vivo could be faithfully mimicked in vitro only in cultured seminiferous tubules, using the active metabolite methoxyacetic acid (MAA). To test whether human testis per se is more sensitive than rat testis to MAA, we compared the responses of cultured rat seminiferous tubules (RSTs) and human testicular tissues (HTT) in vitro. Degeneration in spermatocytes was observed in RSTs 19 hours after a 5-hour exposure to MAA at and above 1 mM. The dying germ cells showed necrotic-like morphology, as seen in vivo. Germ cells in HTT were also killed by doses > or = 1 mM, although the dying germ cells appeared apoptotic, rather than necrotic. For both species, doses lower than 1 mM were without visible effect. Interestingly, agarose gel electrophoresis of DNA from tubules of both species showed internucleosomal DNA fragmentation after MAA treatment, indicating that MAA induced apoptosis in both human and rat germ cells, though the dying cells showed different morphology in the two species. Furthermore, MAA-induced germ cell apoptosis in both species could be significantly attenuated by calcium channel blockers such as nifedipine or verapamil, which inhibit calcium movement through plasma membranes. In conclusion, the results suggest that: 1) human testis is equally sensitive to MAA compared to rat testis; and 2) MAA induces germ cell apoptosis both in human and rat, probably through similar, calcium-dependent mechanism(s). The precise steps in this germ cell apoptosis are under investigation.

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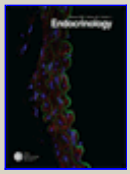

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