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Increased Expression of Estrogen Receptor ß in Pachytene Spermatocytes After Short-Term Methoxyacetic Acid Administration

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Degeneration of primary spermatocytes by apoptosis occurs during normal spermatogenesis, as well as in several pathological conditions, including exposure to specific testicular toxicants. The mechanisms that regulate the death and survival of primary spermatocytes, however, are still not well understood. The recent localization of estrogen receptor beta (ERß) and P450 aromatase in pachytene spermatocytes suggests a role for estrogens in this step of spermatogenesis. Using a well-known model of pachytene spermatocyte apoptosis in adult rats consisting of the administration of methoxyacetic acid (MAA), we investigated the participation of ERß during the initial phase of apoptosis, prior to germ cell loss. Adult rats were treated with a single intraperitoneal dose of MAA, and DNA laddering analysis confirmed apoptotic cell death in the testis. In enriched germ cell fractions and testis from MAA-treated animals, ERß mRNA increased significantly at 3 and 6 hours, respectively. Next, stage-specific induction of ERß mRNA was demonstrated by use of laser capture microdissection of seminiferous tubules in combination with semiquantitative reverse transcription-polymerase chain reaction. The ERß protein also increased significantly after 6 hours and was mainly immunolocalized in the cytoplasm of pachytene spermatocytes of afflicted tubules. The cytoplasmic localization was confirmed by Western blot analysis of isolated cytoplasmic and nuclear fractions of testicular extracts. Finally, the MAA activation of ERß was tested in vitro in HepG2 cells cotransfected with ERß and a reporter construct that contained a consensus estrogen responsive element. Addition of MAA at similar doses used in vivo elicited a similar estrogenic activation as did estradiol at 1 nmol/L concentration. The present results raise the possibility that cytoplasmic ERß participates in the apoptotic process of pachytene spermatocytes induced by MAA. Whether MAA interacts with ERß in the cytoplasm of primary spermatocytes, preventing the progression of the first meiotic division, however, remains to be determined.

Key words: germ cell apoptosis, testicular toxicity, Laser Capture Microdissection

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