

Regulation of ATF4 Gene Expression by Nonylphenol in Mouse Uterus

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Activating transcription factor 4 (ATF4) is a ubiquitous basic leucine zipper transcription factor that is a member of the ATF/cyclic adenosine monophosphate responsive element-binding (CREB) protein family. The expression of many eukaryotic genes is strictly regulated by a series of transcription factor that bind to the *cis*-acting promoter or enhancer elements in a sequence-specific manner. ATF4 is expressed in a wide variety of organs, including the brain, heart, liver, spleen, kidney, lung, thymus, testis and regulate cell proliferation and differentiation in a broad number of tissues. Our previous study showed that ATF4 was up-regulated by estrogen in the mouse uterus. Among the known synthetic environmental estrogens, nonylphenol was know to weakly estrogenic. In order to examine whether nonylphenol have similar effects to the natural hormone, estradiol, we used a mouse model to examine the effects of nonylphenol on ATF4 gene expression and compared it with estradiol by real-time PCR. For the uteri prepare, ovariectomized mice were injected intraperitoneally with a nonylphenol, estrogen every 24h for 3 days and whole uteri (n=4) were collected 6h after the last dosage. Doses of estrogen used 0.3 μg /mouse and nonylphenols used were 50 mg/kg body weight (BW); 5 mg/kg BW; 0.5 mg/kg BW. Real-time PCR results showed that in the uterus, ATF4 was highly expressed in a dose dependent manner by nonylphenol in three orders of magnitude (0.5~50 mg/kg) and ATF4 gene activated by nonylphenol at a high dose (50 mg/kg) were also activated by estrogen (0.3 μg /mouse). These results suggest that the effects of nonylphenol at a high dose (50 mg/kg) were very similar to estrogen (0.3 μg /mouse) in uterine

tissue and ATF4 gene regulated by nonylphenol in the mouse uterus. ATF4 may be involved in nonylphenol induced endocrine disruption in uterus.