Poster #23

Preferential Interaction of PAH-related Compounds with the beta Isoform of the Estrogen Receptor.

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The ability of several 4- and 5-ring polycyclic aromatic hydrocarbon (PAH)-related compounds to interact with the estrogen receptor (ER) alpha and beta isoforms was examined. The compounds, many of which had been previously studied for mutagenic potential, consisted of carbazoles (benzo[a]carbazole and benzo[c]carbazole), benzonaphthothiophenes (benzo[b]naphtho[2,1-d]thiophene and -[2,3-d]thiophene), and several hydroxylated PAHs and thiophenes (2-OH-, 2-OH-5-methyl-, and 8-OH-5-methyl-chrysene; 2-OH-benzo[c]phenanthrene; 3-OH-benzo[b]naphtho[2,1-d]thiophene; and 3-OH-benzo[b]phenanthro[2,3-d]thiophene). Investigations of receptor binding affinity were performed by assessing the ability of the compounds to compete with ^{3}H-labeled 17β-estradiol (E2) for binding to either the D, E, and F domains of human ERα linked to glutathione-S-transferase (GST-hERαdef) or to full-length human ERβ. The ability of the receptor-ligand complex to transactivate ER-regulated genes was assessed using MCF-7 cells transiently transfected with either a Gal4-human ERαdef or Gal4-mouse ERβdef construct, as well as a Gal4-regulated reporter construct. Only those compounds containing a hydroxyl group showed significant binding, which was comparable for both isoforms (IC_{50} range approximately 20-300 nM; E2 IC_{50} approximately 3 nM). However, nearly all compounds were able to induce reporter gene expression preferentially through mERβ. In fact, only in the mERβ system were most compounds able to achieve maximal levels (60-100% of those obtained with E2) at 10 μM, with EC_{50} values ranging from 30-600 nM (E2 EC_{50} approximately 200 pM). These data support previous evidence suggesting that even while some compounds may possess a similar affinity for both ER isoforms, the capacity for transcriptional activation can still be isoform-specific.