Differential Gene Expression Patterns in Developing Sexually Dimorphic Rat Brain Regions Exposed to Antiandrogenic, Estrogenic, or Complex Endocrine - DTU Orbit (21/12/2018)

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The study addressed the question whether gene expression patterns induced by different mixtures of endocrine disrupting chemicals (EDCs) administered in a higher dose range, corresponding to 450×, 200×, and 100× high-end human exposure levels, could be characterized in developing brain with respect to endocrine activity of mixture components, and which developmental processes were preferentially targeted. Three EDC mixtures, A-Mix (anti-androgenic mixture) with 8 antiandrogenic chemicals (di-n-butylphthalate, diethylhexylphthalate, vinclozolin, prochloraz, procymidone, linuron, epoxiconazole, and DDE), E-Mix (estrogenic mixture) with 4 estrogenic chemicals (bisphenol A, 4-methylbenzylidene camphor, 2-ethylhexyl 4-methoxyxycinnamate, and butylparaben), a complex mixture, AEP-Mix, containing the components of A-Mix and E-Mix plus paracetamol, and paracetamol alone, were administered by oral gavage to rat dams from gestation day 7 until weaning. General developmental endpoints were not affected by EDC mixtures or paracetamol. Gene expression was analyzed on postnatal day 6, during sexual brain differentiation, by exon microarray in medial preoptic area in the high-dose group, and by real-time RT-PCR in medial preoptic area and ventromedial hypothalamus in all dose groups. Expression patterns were mixture, sex, and region specific. Effects of the analgesic drug paracetamol, which exhibits antiandrogenic activity in peripheral systems, differed from those of A-Mix. All mixtures had a strong, mixture-specific impact on genes encoding for components of excitatory glutamatergic synapses and genes controlling migration and pathfinding of glutamatergic and GABAergic neurons, as well as genes linked with increased risk of autism spectrum disorders. Because development of glutamatergic synapses is regulated by sex steroids also in hippocampus, this may represent a general target of ECD mixtures.

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