

Down-regulation of early ionotropic glutamate receptor subunit developmental expression as a mechanism for observed plasticity deficits following gestational exposure to benzo(*a*)pyrene

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Abstract

The focus of this study was to characterize the impact of gestational exposure to benzo(*a*)pyrene [B(*a*)P] on modulation of glutamate receptor subunit expression that is critical for the maintenance of synaptic plasticity mechanisms during hippocampal or cortical development in offspring. Previous studies have demonstrated that hippocampal and/or cortical synaptic plasticity (as measured by long-term potentiation and S1-cortex spontaneous/evoked neuronal activity) and learning behavior (as measured by fixed-ratio performance operant testing) is significantly impaired in polycyclic aromatic or halogenated aromatic hydrocarbon-exposed offspring as compared to controls. These previous studies have also revealed that brain to body weight ratios are greater in exposed offspring relative to controls indicative of intrauterine growth retardation which has been shown to manifest as low birth weight in offspring. Recent epidemiological studies have identified an effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children [Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environ Health Perspect* 2006;114:1287–92]. The present study utilizes a well-characterized animal model to test the hypothesis that gestational exposure to B(*a*)P causes dysregulation of developmental ionotropic glutamate receptor subunit expression, namely the *N*-methyl-D-aspartate receptor (NMDAR) and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor (AMPA) both critical to the expression of synaptic plasticity mechanisms. To mechanistically ascertain the basis of B(*a*)P-induced plasticity perturbations, timed pregnant Long-Evans rats were exposed in an oral subacute exposure regimen to 0, 25 and 150 μ g/kg BW B(*a*)P on gestation days 14–17. The first sub-hypothesis tested whether gestational exposure to B(*a*)P would result in significant disposition in offspring. The second sub-hypothesis tested whether gestational exposure to B(*a*)P would result in down-regulation of *early* developmental expression of NMDA and AMPA receptor subunits in the hippocampus of offspring as well as in primary neuronal cultures. The results of these studies revealed significant: (1) disposition to the hippocampus and cortex, (2) down-regulation of developmental glutamate receptor mRNA and protein subunit expression and (3) voltage-dependent decreases in the amplitude of inward currents at negative potentials in B(*a*)P-treated cortical neuronal membranes.

These results suggest that plasticity and behavioral deficits produced as a result of gestational B(*a*)P exposure are at least, in part, a result of down-regulation of *early* developmental glutamate receptor subunit expression and function at a time when excitatory synapses are being formed for the first time in the developing central nervous system. The results also predict that in B(*a*)P-exposed offspring with reduced *early* glutamate receptor subunit expression, a parallel deficit in behaviors that depend on normal hippocampal or cortical functioning will be observed and that these deficits will be present throughout life.

Keywords: B(*a*)P metabolite; Gestational exposure; Electrophysiology; Cortex; Hippocampus; Long-Evans rats; Long-term potentiation; Spontaneous/evoked activity; AhR imprinting