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Estrogen Receptor Independent Neurotoxic Mechanism of Bisphenol A, an Environmental Estrogen: Association of ERK Activation and NF-kB Inactivation

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Bisphenol A (BPA), a ubiquitous environmental contaminant has been shown to cause developmental toxicity and carcinogenic effect. BPA may do physiological action through estrogen receptor (ER-α and ER-β) which are expressed in central nerve system. We previously found that expose of BPA to immature mice resulted in behavior alternation, suggesting that overexposure of BPA could be neurotoxin. In this study, we further investigated molecular neurotoxic mechanisms of BPA. BPA concentration dependently (more than 50 mM) increased vulnerability (decrease of cell viability and differentiation, and increase of apoptotic cell death) of undifferentiated PC12 cells and cortical neuronal cells isolated gestation 18 day's embryos. The ER antagonists, ICI 182, 780 and tamoxifen did not block these effects. The cell vulnerability against BPA was not significantly different in the PC12 cells over expressing ER compared with PC12 cells expressing vector alone or stimulated by only lipofectamine. In addition, there is no difference between BPA and 17-β estradiol, a well known agonist of ER receptor in the induction of neurotoxic responses. However, consistent with dose dependent increased neuronal cell susceptibility, BPA significantly activated ERK2 but inhibited anti-apoptotic NF-κB activation. Moreover, ERK specific inhibitor PD 98,059 reversed BPA-induced cell death. This study demonstrated that exposure of certain level of BPA (more than 50 mM) may interfere normal neuronal cell differentiation, and thereby cause neuronal cell death which may eventually be related with the behavior alternation in vivo. However, this neurotoxic effect may not be directly mediated through ER receptor but ERK2/NF-κB pathway may be involved in BPA-induced neuronal toxicity.

Keyword : BPA, neurotoxic mechanism