Mechanisms and roles of embryonic midbrain cell differentiation and apoptosis in the ochratoxin-A induced microcephaly

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The mycotoxin ochratoxin A (OTA) is a natural contaminant present in feed and food. It has been reported that OTA frequently produces microcephaly in mice and rats exposed *in utero* during gestation. The developing brain appears to be the most susceptible targets to environmental chemicals at the early organogenesis as observed in teratogenic studies. In this study, we first confirmed that OTA induced microcephaly in cultured embryo as seen in vivo. Since the significance of the relationship between embryotoxicity and changing of cell behaviors such as cell death and differentiation in the organogenesis of embryos has been proposed, we examined whether induction of cell death and inhibition of cell differentiation during the organogenesis is involved in the OTA-induced microcephaly. Involvement of transcription factors AP-1 and NF-kB activation in the OTA-induced toxicity was also examined in cultured embryonic midbrain cells. OTA dose dependently increased DNA fragmentation, an indicator of apoptosis and inhibited cell differentiation. Consistent with its effect on cytotoxicity (inhibition of cell differentiation and induction of apoptosis), OTA clearly increased AP-1 and NF-*k*B activation. OTA-induced inhibition of cell differentiation and the activation of AP-1 and NF-*k*B was diminished in the cells treated with 15-deoxy-PGJ_2, a peroxisome proliferator activator receptor-ganmma agonist. These results show that inhibition of cell differentiation and induction of apoptosis are implicated in the OTA-induced microcephaly, and 15-deoxy PGJ_2 blocks OTA-induced neurotoxicity by inhibiting AP-1 and NF-*k*B activation in cultured rat embryonic midbrain cells.