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Editorial Open Access

Possible Neuronal Toxin in Plastics Discarded in Rivers and the Ocean

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Editorial

The plastic products originating from disposal of bottle, container, or knife, in inland cities enter rivers and may reach the ocean and islands. They turn to nano- or microplastics. There have been attempts to reduce the effect of this environmental pollution on humans. For example, plastic straws used for drinks have been changed to natural material in some parts of the United States. However, plastics still affect human organs, in part due to bisphenol A (BPA), which is included in plastics as a plasticizer. BPA is an endocrine disrupting chemical (EDC) that promotes a female-inducing phenotype in genital organs *via* estrogen receptors. BPA is a typical EDC that can cross the blood-brain barrier (BBB) due to its hydrophobic character [1], and neurons or glial cells can be affected in a BPA-specific manner [2].

We have found that BPA-like alkylphenol compound can cause apoptosis in PC12 cells [3]. This mechanism was classified as endoplasmic stress (ER)-mediated apoptosis due to involvement of accumulation of unfolded proteins with upregulation of glucose-regulated protein 78 (GRP78) / BiP (immunoglobulin heavy-chain binding protein), a marker of ER stress [4].

In cell-based assays, we have shown that BPA is an inducer of neurite outgrowth in PC12 cells. Contrary to expectations, we also found that the neurites are unique compared with those induced by nerve growth factor (NGF). This suggests that BPA may have a direct function in differentiation of neurons. This evidence was obtained using neuronal marker proteins such as NeuroD, Tuj1, and Map2. In addition to functional formation of neurites in PC12 cells, BPA administered to pregnant rats causes the post-natal rat to have damaged memory and actions [5]. Surprisingly, we found that BPA mimicked the function of NGF, which suggests the potential for discovery of further findings.

A morphological analysis showed that the shape of BPA-treated cells was the same as that of forskolin-treated cells (manuscript in submission). Forskolin promotes neuronal differentiation *via* the PKA-CREB (cAMP response element binding protein) signaling pathway, in which PKA activated by forskolin phosphorylates CREB, which then binds to CRE sites in various gene promoters (manuscript in submission). This process also involves acetylation of specific amino acids in histones, which induces expression of the orphan nuclear receptor *nur77* gene, an immediate early gene (manuscript in submission), and leading to epigenetic regulation of gene expression. Histone acetyltransferases, which induce gene expression by acetylation of specific amino acid residues in histones, and histone deacetylases, which suppress gene expression by deacetylation of histones, are involved in this process.

Based on these results, we suggest that intracellular signalling caused by BPA is similar to forskolin-induced signaling, while BPA shares a binding site on a nuclear receptor with endogenous hormones. Regarding histone modification, it is well known that mono-, di- or trimethylation of specific lysine residues is important for epigenetic regulation of gene expression. Moreover, it is still unclear if methylation or demethylation controls epigenetic gene expression with regard to organ- and cell-specific phenomena. A further study is needed to examine whether a BPA-mediated signal leading to neurite extension prevents harmful effects of BPA on neurons or neuronal networks.

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