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Epigenotoxic effects of Bisphenol-A mediated by its metabolite reducing DNA methylation

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Bisphenol-A (BPA) is commonly used in the manufacture of polycarbonate plastics and epoxy resins and is known to possess a weak estrogenic activity. BPA is also an environmental contaminant with adverse health effects suspected to be mediated through epigenetic mechanisms. We have reported that the FLO1-dependent flocculation of transgenic yeast transformed with human DNA methyltransferase genes (DNMT yeast) is a useful tool in epigenotoxicology studies. In this study, we have examined the effects of BPA in the presence of metabolic activation (S-9 mix) on the transcription level of the FLO1 gene in the DNMT yeast. In the presence of S-9 mix, BPA reduced the intensity of reporter green fluorescence protein (GFP) driven by the FLO1 promoter. The metabolite of BPA 4-methyl-2,4-bis(p-hydroxyphenyl)- pent-1-ene (MBP) also exhibited similar effect on this promoter activity. Moreover, BPA in the presence of S-9 mix showed only a weak while MBP had no inhibitory activity on the expression of GFP reporter gene controlled by a modified FLO1 promoter lacking some CpG sites. FLO1 mRNA expression level was also decreased by both S-9 mix activated BPA and MBP. Furthermore, the global DNA methylation level in the human HEK293 cells was reduced by MBP as well. These results indicate that BPA metabolites, including MBP, have inhibitory effect on DNA methylation. Our DNMT yeast assay provides a novel in vitro method for screening for chemicals that can alter the epigenome also by a mechanism dependent on their metabolic activation.

Keywords:
Bisphenol-A; metabolite; DNA methylation.