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C/EBPb Activation By Oltipraz, A Cancer Chemopreventive Agent, Inhibits CYP1A1 Induction by Polycyclic Aromatic Hydrocarbon

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Oltipraz, a cancer chemopreventive agent, induces CYP1A1 to a certain extent by transactivation of the gene via the Ah receptor (AhR)-xenobiotic response element (XRE) pathway. Previously, we showed that glutathione S-transferase induction by oltipraz involves CCAAT/enhancer binding protein β (C/EBPβ) activation. Given that oltipraz activates C/EBPβ for gene transactivation and that the putative C/EBP binding site is located in the *CYP1A1* promoter region, this study investigated the effect of oltipraz on CYP1A1 induction by 3-methylcholanthrene (3-MC). CYP1A1 was induced by 3-MC in H4IIE cells in a time- and concentration-dependent manner. Gel shift analysis showed that 3-MC increased the protein binding to the XRE. Immunocompetition analysis verified the specificity of AhR-XRE binding. Oltipraz treatment (30 μM) induced CYP1A1 and CYP1A1 promoter-luciferase gene and increased AhR-XRE binding activity, which were 10-20% of those in 3-MC (100 nM)-treated cells. However, AhR-XRE binding was not increased after 10 μM oltipraz treatment. CYP1A1 and CYP1A1-luciferase gene induction by 3-MC were both significantly inhibited by 10 μM oltipraz treatment. AhR DNA binding was also suppressed by oltipraz. Oltipraz enhanced protein binding to the C/EBP binding site in the gene promoter and the binding complex comprised of C/EBPβ and partly C/EBPδ. Overexpression of dominant-negative mutant C/EBP significantly abolished the ability of oltipraz to suppress 3-MC-inducible CYP1A1 and CYP1A1-reporter gene expression. Consistently, C/EBPβ overexpression blocked CYP1A1-reporter gene induction by 3-MC. These results provided evidence that oltipraz suppresses polycyclic aromatic hydrocarbon (PAH) induction of the *CYP1A1* gene and that activation of C/EBPβ by oltipraz contributes to suppression of PAH-inducible AhR-mediated CYP1A1 expression.

Keyword : Cancer Chemoprevention, Oltipraz, CCAAT/Enhancer Binding Protein β (C/EBPβ), CYP1A1, Polycyclic aromatic hydrocarbons (PAHs)