SEX DIFFERENCES IN THE RESPONSE TO PAH AND RISK OF LUNG CANCER

Aage Haugen¹, Steen Mollerup¹, Heidi Uppstad¹, David H. Phillips², Shan Zienolddiny¹ and Helge Lind¹

¹Section of Toxicology, Department of Chemical and Biological Working Environment, National Institute of Occupational Health, PO Box 8149 Dep, 0033 Oslo, Norway
²Section of Molecular Carcinogenesis, Institute of Cancer Research, Surrey SM2 5NG, UK

Abstract: Many of the substances humans are exposed to in the environment pose a health risk. Thus, there is a need to come up with strategies to understand the mechanisms by which toxic substances impair human health. A few animal and human studies have examined the role of sex and sex hormones in toxicology studies. Molecular studies have pointed to sex differences in the metabolism of polycyclic aromatic hydrocarbons (PAH). We have reported higher levels of PAH-DNA adducts in the lungs of females compared to males although the females had smoked less. When expressing PAH-DNA adduct level in relation to smoking dose we found that adducts/pack year and adducts/cigarette/ day were significantly higher among females. The expression of genes in the PAH bioactivation pathway was investigated. CYP1A1 was significantly increased in smokers compared to ex-smokers and never smokers; CYP1B1 was also increased in smokers although to a lesser extent than CYP1A1. When analyzed in relation to sex, current smoking females had a 3.9 fold higher median level of CYP1A1 mRNA compared to current smoking males. Lung DNA adducts were significantly related to CYP1A1 irrespective of smoking-status. No indication of sex differences in CYP1B1 expression were found in any smoking category. Our data also suggest that intrinsic differences in the capacity to bioactivate PAH in human lung cells may exist. Lung adenocarcinoma cell lines isolated from women showed significantly higher constitutive and induced expression of CYP1A1 mRNA compared with cell lines derived from men. This correlated with increased formation of DNA-adducts in response to BaP-exposure in cell lines from women. For CYP1B1 no apparent differences were observed, confirming our in vivo data. Estrogen-regulated events affecting the lung or handling of lung carcinogens could exert selective effects on women. Estrogen receptors are expressed in the lung. Down regulating ERα/β by siRNA resulted in altered constitutive and induced expression of CYP1A1 indicating a role of these receptors in lung carcinogenesis. Estrogen signaling has been shown to regulate MDM2 expression levels. Data indicate that even small changes in MDM2 levels can affect the p53 pathway and cancer development. Our results indicate that the G/G genotype of SNP309 found in the promoter of the MDM2 gene regulated by hormonal signaling pathways are associated with lung cancer risk and interacts with sex and tumor p53 mutation status. Together these data suggests that females are particularly susceptible to the carcinogenic effect of PAH and the mechanisms underlying the sex differences in lung cancer risk are likely to be multifactorial.

Key words: PAH, susceptibility, CYP1A1, CYP1B1, estrogen, MDM2

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