3-Aminobiphenyl and 4-aminophenyl hemoglobin adducts in adult smokers and nonsmokers phenotyped for CYP1A2 and NAT2 activity.

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Aromatic amines found in cigarette (cigt) smoke and other sources have been suggested to be carcinogenic due to activation of the N-hydroxyl metabolites formed by CYP1A2. Hemoglobin adducts of 3-aminobiphenyl (3-ABP Hb) and/or 4-aminobiphenyl (4-ABP Hb) may be used to monitor cigt smoke exposure. It has been suggested that 3-ABP Hb is a more specific biomarker of cigt smoke exposure. Slow acetylators have been found to exhibit higher amounts of the Hb adducts due to inefficient acetylation. The goal of this study was to determine the role of CYP1A2 and NAT2 phenotype on 3-ABP and 4-ABP Hb adducts and to determine the intra- and inter-individual variability in the adduct levels. The study was conducted in adult smokers (S, n=72) smoking at least one cigt (3-6.9 mg FTC tar range) every day for over the last 12 months, and nonsmokers (NS, n=68). The subjects were phenotyped for CYP1A2 and NAT2 using urinary caffeine metabolites. Blood samples were collected to measure levels of 3-ABP Hb and 4-ABP Hb twice within 6 weeks (wk) by capillary GC-MS. The CYP1A2 activity [ratio of (1,7-methyluric acid + 1,7-dimethylxanthine)/(1,3,7-trimethylxanthine)] was higher ($p<0.001$) in S (6.8 $\pm$3.71) compared to NS (4.07 $\pm$2.59). A bimodal distribution was observed for the NAT2 activity [(5-acetylamino-6-formylamino-3-methyluracil, AFMU)/ (1-methylxanthine)] indicating slow and fast acetylators. No differences were observed in NAT2 activity, between S and NS. The levels of 4-ABP Hb adducts were significantly ($p<0.0001$) greater in S (32.4 $\pm$17.8 pg/g Hb) compared to NS (7.8$\pm$4.9 pg/g Hb). The levels of 3-ABP Hb adducts (3.4 $\pm$3 pg/g Hb) while significantly greater ($p<0.05$) in S compared to NS were about 10-fold lower in S compared to 4-ABP Hb adducts in the same group. There was no difference in both the adduct values when compared between the two weekly measurements for the same individuals. Intra-individual variability (%CV) obtained by comparing Hb adduct levels from wk 1 to wk 6 was ~23% for 3-ABP and ~19% for 4-ABP Hb adducts. Significant correlation ($p<0.001$) was observed for both 3-ABP and 4-ABP Hb adducts with number of cigts smoked. Evaluation of the relationship between 3-ABP and 4-ABP Hb adducts ($r^2=0.69$) suggests that the exposure to one or both aromatic amines is from other sources in addition to cigts. The levels of 4-ABP Hb adducts appeared to increase with CYP1A2 activity ($r^2=0.20$) whereas this relationship was much weaker with the 3-ABP Hb adducts ($r^2=0.06$). The lack of correlation between the Hb adducts in slow and fast acetylators, suggest that acetylator phenotype has no influence on ABP Hb adducts. Although there appears to be less confounding factors in the measurement of 3-ABP Hb adducts in nonsmokers, its utility as a biomarker of exposure to cigarette smoke is limited due to the low levels observed in smokers. The lack of significant differences between measurements taken on week 1 compared to week 6 suggests that a single blood sample would be adequate to monitor current exposure.