Alteration of Substrate Specificity by Mutations on Flavin-Containing Monooxygenase 3 (*FMO3*) Gene in Man

Ju-Hee Kang, Chang-Shin Park, Woon-Gye Chung,
Dong-Kyun Park[1] and Young-Nam Cha

Dept. of Pharmacology and Toxicology, Inha Univ., [1]Dept. of Internal Medicine, Gachon Medical School, Inchon, Korea

In previous studies, we found a significant correlation between the activities of ranitidine *N*-oxidation catalyzed by flavin-containing monooxygenase (FMO) and the presence of mutations in exon 4 (Glu158Lys) and exon 7 (Glu308Gly) of *FMO3* gene in Korean volunteers. However, the caffeine *N*-1 demethylase activities catalyzed also by FMO3 were not significantly correlated with these *FMO3* mutations. Results of present study show that another mutation in exon 6 of *FMO3* (Val257Met), which occurs commonly in our Korean population, is significantly correlated with the *N*-1 demethylation of caffeine but not with the *N*-oxidation of ranitidine.

The exon 6 mutation in *FMO3* was caused by a point mutation (G769A) and was observed commonly (17.1% allele frequency) in our Korean population (n=197). This point mutation in *FMO3* brings about a substitution of Val^{257} to Met^{257} and transforms the secondary structure of FMO3 from a sheet to a helix structure. Presence of this mutant allele was correlated significantly with the reduced FMO activity catalyzing the *N*-1 demethylation of caffeine producing the bromine but was not correlated with the FMO activity catalyzing the *N*-oxidation of ranitidine producing ranitidine *N*-oxide. The low FMO activity (*N*-1 demethylation of caffeine) observed in a family of a person showing heterozygous nonsense mutation in exon 4 (Gly148Stop) and heterozygous missense mutation in exon 6 (Val257Met) of *FMO3* could be explained by the inheritance of exon 6 mutation but not by the inheritance of exon 4 and/or exon 7 mutations. Results of these human studies suggest that different point mutations in the coding regions of *FMO3* could alter the secondary structure of FMO3 and this, in turn, may alter the substrate specificity. Result further suggest that phenotyping people for their FMO3 activity need to be conducted with several probe compounds of varying chemical structure that correlate with each mutation on the *FMO3* gene.