Sex, Smoking, and Pharmacogenetics Impact Metabolism of the Oral Toxicant Arecoline

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Background/Objectives: Arecoline is a substance of abuse and major contributor towards premalignant/malignant oral disorders in areca (betel) nut users. Millions of people ingest copious amounts of arecoline during areca chewing, daily, but little is known about factors impacting arecoline metabolism (hydrolysis) in the body. This study investigated the influence of sex, pharmacogenetics, and tissue sites on arecoline hydrolysis.

Experimental Methods: Physiologically simulated incubations were performed at 37°C with buffered micro-suspensions containing arecoline (25–100μM) and test variable: (1) Carboxylesterase genetic variant (CES1c), or (2) Pooled tissue/saliva samples from male and female donors. Following all incubations, formation of arecaidine (a major arecoline metabolite) was measured by HPLC-PDA. Arecoline hydrolase activity (metabolic rate) was statistically compared between groups using a two-tailed Student's *t*-test. All sample batches were run in at least quadruplicate.

Results: For all tested arecoline concentrations, samples containing the genetic variant CES1c exhibited a significantly lower arecoline metabolic rate compared to wild-type CES1, ranging from -73.0% to -77.5%($p<0.0001$). In human liver S9, a greater arecoline metabolic rate in female samples, compared to male samples, was observed across all arecoline concentrations, ranging from +18.8% to +23.3%($p<0.01$). Although arecoline metabolism was undetected in human intestine, kidney, or saliva samples, a significant uptick (+204%;$p<0.0001$) in lung metabolism was found in smokers compared to non-smokers. This finding may be significant in individuals vaping arecoline. Furthermore, hepatic S9 from female mice(+71.3%;$p=0.0003$) and guinea pig(+24.7%;$p=0.0008$) exhibited a greater arecoline metabolic rate than male samples. Conversely, male rat(+81.0%;$p=0.0087$) and rabbit(+14.4%;$p=0.001$) samples had a higher metabolic rate than female samples.

Conclusion: Our work has uncovered inter-species variation and sex as a plausible biological variable impacting arecoline metabolism. In humans, males may be more prone to arecoline-induced toxicities. Furthermore, individuals expressing the CES1c pharmacogenetic variant may be at higher risk of exposure and toxicities following arecoline consumption.

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