Nicotine, Cotinine or a cotinine metabolite inhibits HNF4-induced DNA-strand break in metabolically competent hepatic cells

Patricia Ordonez1, Ana Belen Sierra, Ali Suraya, Oscar M. Camacho, Anishita Banerjee, Andrew Baxter, David Waters, Emmanuel Minet1

1Nutricia Research S.L., Santiago Cotobade 2, Tres Cantos, Madrid, Spain.
2Department of Pharmacology and Therapeutics, Division of Health Sciences, University of Edinburgh, Edinburgh, EH9 3JY, UK.

Background: Nicotine has been associated with increased cancer risk, particularly in the setting of combined tobacco and alcohol use. To better understand the underlying mechanisms, we have examined the effects of nicotine and cotinine on HNF4, a transcription factor involved in the regulation of DNA repair. We used HNF4 reporter cell lines and primary human hepatocytes to investigate the role of cotinine and its metabolites in the regulation of DNA repair.

Methods: Primary human hepatocytes were isolated from liver biopsies and cultured as monolayers. Cotinine was added at concentrations of 10, 50, and 100 μM for 18 hours. After treatment, cells were harvested and subjected to flow cytometry analysis for the detection of apoptosis. The effect of cotinine on the expression of HNF4 was also evaluated by Western blotting.

Results: Cotinine treatment led to a significant decrease in the expression of HNF4, as evidenced by Western blotting. Flow cytometry analysis showed a significant increase in the percentage of apoptotic cells in the cotinine-treated group compared to the control group.

Conclusions: Our results suggest that cotinine may have a role in the regulation of DNA repair and apoptosis. Further studies are needed to understand the mechanisms involved.