

## Sex-dependent gene expression of kidney transporters after ochratoxin A exposure in F344 rats

Laura Pastor, Ariane Vettorazzi, Adela López de Cerain

Department of Pharmacology and Toxicology, School of Pharmacy, University of Navarra, Pamplona, Spain.

Ochratoxin A (OTA) is a mycotoxin produced by fungi of the genera *Aspergillus* and *Penicillium*. It contaminates several food commodities such as cereals, nuts and spices. It is considered as a potent renal carcinogen in rodents but its mechanism of action is still not understood. It is well known that rats are considerably more sensitive than mice. Moreover, a high susceptibility of male rats to tumour formation has been demonstrated. It has been hypothesized that sex- and species-differences in OTA-mediated toxicity might be due to variations in transport mechanisms in kidney cells. According to this, some renal transporter families, which can be responsible for OTA transport, have demonstrated sex differences and also variations in their expression levels after OTA exposure. Therefore, the aim of this study was to analyze, by RT-qPCR, renal transporters expression in 15-week-old male (M) and female (F) F344 rats at basal level and after single oral OTA administration (0.50 mg/kg bw). Temporal profiles (24h, 48h, 72h, 96h, 1 and 2 months) were studied per sex and transporter.

Oatp1 (M>F), Oat2 and Pept2 (F>M) sex-differences were confirmed at basal level. Moreover, a high Bcrp expression was observed in males. After OTA exposure, females showed a general decrease in all transporters studied, mainly after 48 hours. In males, expression changes were observed after 24 hours and mainly in apical proteins; besides, at 48 hours, an increase in Oat2 expression (reabsorption transporter) and a decrease of Mrp2 and Bcrp (exclusion transporters) were also observed.

While similar time-profiles were determined for Abc, Oatp (Slco1) and Pept (Slc15) families, the highest sex differences involved Oat (Slc22) transporters. Oat2, Oat3 and Oat5 expression showed a significant increase in males while Oat1, Oat2 and Oat5 level decreased considerably in females. These molecular changes might be implicated in the highest male susceptibility to OTA renal carcinogenesis.