Sex- and time-dependent gene expression profile in kidneys of F344 rats after repeated OTA oral administration

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Ochratoxin A (OTA) is a natural mycotoxin produced by *Aspergillus* and *Penicillium* species with important implications for health. It is one of the most potent renal carcinogens studied in rodents, producing a higher incidence of tumors in male than in female rats. The aim of this study was to determine kidney gene expression profiles, to identify the pathways that may lead to these sex differences. For that purpose, male and female F344 rats were treated with a daily oral dose of 0.50 mg OTA/kg bw for 7 or 21 days. Gene expression was studied at basal level (male vs female controls) and after OTA treatment (treated vs control, per sex and timepoint).

In control groups, similar number of differentially expressed genes (DEG) showed sex-biased expression and 50% genes were common. 12 ToxLists were significantly altered and they were related with xenobiotic metabolism signaling, fatty acid metabolism, renal damage, nuclear factors signaling and cytochrome P450 panels.

OTA treatment increased the number of DEG over time in both sexes. In females, 528 and 2648 were DEG after 7 and 21 days respectively, and in general, a slightly tendency to downregulation was observed. In addition, 86.2% of total genes modified after 7 days were also altered after 21 days and showed the same pattern. In contrast, a higher response was observed in males than in females after 7 days, which was also different compared to 21 days. After 7 and 21 days 1088 and 2404 were DEG, but only 277 genes were common. Moreover, 82.3% of genes were upregulated after 7 days and a few of these common genes tended to downregulation after 21 days.

Less than 5% of altered genes of all groups, presented -1.5<logFC<1.5. Interestingly, the most sex-biased genes in control animals tended to be strongly downregulated in their predominant sex after OTA treatment: CYP2C9 and CYP27B1 in males and Akr1b7 and Ly6a in females.

Finally, concerning the ToxLists, females showed a similar response at both timepoints (21 common lists of 26 or 32): OTA produced changes in renal damage and toxicity, xenobiotic metabolism signaling and anti-oxidative response lists. Regarding males, 7 days group showed only 11 altered lists, being nuclear receptor signaling and glutathione depletion strongly modified. However, after 21 days, 37 lists were altered and renal damage, proliferation, fatty acid metabolism and AhR signaling were the most modified lists.