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Does ochratoxin A (OTA) cause testicular cancer in humans?

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Ochratoxin A (OTA) is a naturally occurring contaminant of cereals, pigmeat, and other foods and is a known genotoxic in animals. It is a nephrotoxin and a carcinogen associated with Balkan endemic nephropathy and urinary tract tumours. It is also thought to be a cause of testicular cancer. A previous study has shown that consumption of foods contaminated with ochratoxin A during pregnancy induces lesions in testicular DNA of male offspring, and this supports a possible role for OTA in testicular cancer. Additionally, prenatal exposure to ochratoxin A in mice significantly depresses expression of the DMRT1 gene in male offspring, and the loss of this gene produces germ cell testicular tumours in mice. This molecular evidence supports the theory that ochratoxin A might be related to germ cell testicular tumours in mice and in humans.

Key words: ochratoxin A, testicular cancer, mycotoxins

Mycotoxins are fungal secondary metabolites that have been associated with severe toxic effects on vertebrates, produced by many important phytopathogenic and food spoilage fungi including *Aspergillus*, *Penicillium*, *Fusarium*, and *Alternaria* species. The contamination of foods and animal feeds with mycotoxins is a worldwide problem (1). Ochratoxin A (OTA) is a mycotoxin which is produced by some species of Aspergillus such as *Aspergillus ochraceus*, mainly in tropical regions, and by Penicillium species like *Penicillium verrucosum* or *Penicillium viridicatum*; chemically, it is a derivative of isocumarine linked to L-phenylalanine (2). The mycotoxin is frequently found as a contaminant in grains or in other plant products such as red wine, coffee beans, nuts, and several spices. High levels of OTA are present in some animal-derived food, especially pork products, through "carry-over" – the consequence of feeding moldy fodder to non-ruminant animals (3). The meat of ruminants, e. g., cows, contains little OTA because OTA is cleaved by the protozoan and bacterial enzymes that are present in the rumen. Nevertheless, OTA occurs in the milk of cows that have been exposed to large quantities of OTA (4).

Currently, OTA is one of the most relevant mycotoxins, its presence in food and feed products being regulated in many countries (5). Oral LD50 values are 1.0–6.0 mg/kg for pigs, 20–30 mg/kg for rats and 48–58 mg/kg for mice (5, 6). OTA is considered to be a cumulative toxic compound since it is easily absorbed through the stomach and the small intestine but hardly eliminated through the biliary and urinary routes. Oral OTA half-lives are 35.5 days for humans, 21 days for monkeys, 72–120 hours for pigs, 55–120 hours for rats and 40 hours for mice (5, 6).

A tolerable daily intake (TDI) value of 5 ng OTA/kg bw / day is recommended by the World Health Organization since it has toxic effects and is found in human blood and in breast milk, thus confirming human exposure (5, 7). It is known mainly for its nephrotoxicity (5). In addition, OTA has mutagenic, teratogenic, neurotoxic, hepatotoxic and immunotoxic properties (6).

OTA is classified as possibly carcinogenic to humans (group 2B) since there is evidence for experimental animals but not for humans (5, 7). Previous studies have shown that OTA is a testicular toxin (8–10). OTA is also believed to be a cause of testicular cancer. Gary G. Schwartz (2002) had hypothesized that exposure to OTA-contaminated food provides a rational explanation for much of the descriptive epidemiology of testicular cancer; it could induce adducts in testicular DNA and is a known genotoxic carcinogen in animals. Hence, OTA is a biologically reasonable cause of testicular cancer (11).

In a recent study, this hypothesis was proved experimentally by intrauterine exposure to OTA (2.5 mg/kg/b.w) which produced DNA adducts in the testes of newborn mice; these adducts are similar to the DNA adducts that are observed in the kidney and testes of adult mice exposed to OTA via the diet (12). However, this finding was debated by Peter G. Mantle (13) who indicated the previous literature to have clearly demonstrated that OTA did not cause testicular tumours in rats or in mice, even when a high dose exposure severely constrained growth (14) and provided an approximately six times higher daily OTA exposure than in the study done by Jennings-Gee et al. (12) without causing testis tumours. Furthermore, there is an indirect support of the above from an NTP study on fumonisin B1 (15), in which testicular cancer was naturally common in ageing control male rats and similarly in response to an increasing exposure to that toxin. There were no testis tumours in male mice, either.

Schwartz et al. (16) substantiated the finding reported in (12) by explaining the recent research which has shown that prenatal exposure to ochratoxin A in mice significantly depresses the expression of the DMRT1 gene in offspring, particularly in male offspring (17). DMRT1 is a doublesex and mab-3-related transcription factor expressed in Sertoli cells and undifferentiated spermatogonia of the postnatal testis (18). DMRT1 is a tumour suppressor gene in the testis; loss of this gene produces germ cell testicular tumours in mice (19) and humans (20).

Hence, a significant molecular evidence supports the hypothesis that ochratoxin A may be causally related to germ cell testicular tumours in mice and in men. Future epidemiologic and molecular studies in humans are needed to draw a conclusion whether OTA is a causative agent in testicular cancer.

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AR OCHRATOKSINAS A SUKELIA ŽMONĖMS SĖKLIDŽIŲ VĖŽĮ?

Santrauka

Ochratoksinas A (OTA) yra natūralus taršalas, randamas grūduose, kiaulienoje ir kituose maisto produktuose, kurio genotoksiškumas gyvūnams yra žinomas. Šis karcinogenas yra susijęs su Balkanų endemine nefropatija ir šlapimo takų navikais. Manoma, kad jis gali būti ir sėklidžių vėžio priežastis. Ankstesnėse studijose nurodoma, kad ochratoksinu užteršto maisto vartojimas nėštumo metu sukelia sėklidžių DNR pažeidimus – taigi turi įtakos sėklidžių vėžio atsiradimui, be to, reikšmingai sumažina DMRT1 geno ekspresiją vyriškuose palikuonyse, o tai sukelia pelių embriogeninių ląstelių sėklidžių navikus. Šis molekulinis įrodymas pagrindžia teoriją, kad ochratoksinas A gali būti susijęs tiek su pelių, tiek ir žmogaus sėklidžių embriogeniniais navikais.

Raktažodžiai: ochratoksinas A, sėklidžių vėžys, mikotoksinai